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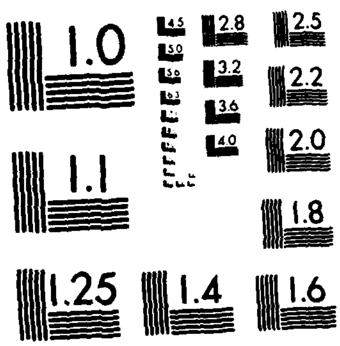
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SUFFIELD REPORT

NO. 403

AD-A171 509

"P R O B I T": A PROBIT ANALYSIS PROGRAM FOR THE DRES COMPUTER FACILITY (U)

by

J. McFee, C.E. Mendoza,
J. Smith and D. Rigby

Project No. 051SB

July 1985

DEFENCE RESEARCH ESTABLISHMENT SUFFIELD, RALSTON, ALBERTA

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ABSTRACT

This report describes an interactive computer program, PROBIT, which performs automated probit analysis. The code is written in the FORTRAN IV language using a modified iterative maximum likelihood algorithm and runs on the DRES Honeywell DPS-8/70 and VAX 11/780 computers.

A series of tests were performed to compare PROBIT with other probit analysis programs. These include the old DRES PROBT (modified IBM PROBT) and programs contained in the commerical statistical packages S103 and SAS. PROBIT clearly outperformed DRES PROBT and performed as well as S103 and as well or slightly better than SAS.

The input methods and output format of PROBIT can be modified whereas those of most commerical statistical packages cannot. Finally, PROBIT cost substantially less to develop than the purchase price of typical commerical statistical packages containing a good probit analysis program.

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ACKNOWLEDGEMENT

The technical advice of Ms. P. Morse, Central Experiment Station, Agriculture Canada, Ottawa, concerning probit analysis in general and specific probit analysis programs is gratefully acknowledged.

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1.0 INTRODUCTION

There are numerous ways to quantify the effect of a substance on an organism. One of the most widely used is the ED_{50}, the quantity of substance which produces the effect of interest in 50% of the population.

Most experimental designs used to determine the ED_{50} consist of a finite number of treatment groups, each of which comprises a finite number of organisms. Origanisms within each group are given the same quantity of substance and the quantity differs from group to group. Usually the number of treatment groups and the number of organisms within a group are small (<10).

A variety of methods exists to estimate ED_{50} levels from the data. These include the methods of extreme lethal doses, the Dragstedt-Behrens method, Reed-Muench, Spearman-Karber, moving average, and probit analysis (Finney 1971). Of these, only probit analysis is completely self consistent. The other methods will commonly give the same answer as probit analysis, but lead to serious errors if the dose range is very asymmetric about $\ln(ED_{50})$.

There are several methods for performing probit analysis. Some are graphical and therefore not readily suited for automated data analysis. Others cannot estimate ED levels other than the ED_{50} or do not determine uncertainties of estimated quantities. A complete discussion of the various ways of estimating ED levels may be found in Finney (1971).

In the past, DRES carried out probit analysis using a program, PROBT (Chenier et al. 1962), based on a modified form of the subroutine PROBT (IBM PROBT)[1] which is contained in the IBM Scientific Subroutine Library[2]. The subroutine is based on a modified version of the iterative maximum likelihood method of Finney (1971). This is a popular method for automated probit analysis since it requires no further user intervention once data has been provided and is quite robust. (Robustness of an algorithm or program is a measure of its ability to converge rapidly to a solution, and to function without producing meaningless numbers or encountering fatal errors.) A number of faults had been demonstrated with the DRES PROBT program. DRES PROBT did not function well with data sets which included a number of null and/or 100% response rates. Further, the program calculated only the ED_{50}; whereas in some applications, other ED levels such as the ED_{1}, $E9_{95}$ or ED_{99} were often required. Recently, it was also found that the code contains errors in calculation. These included incorrect estimates of the number of degrees of freedom and the variance of the regression slope, as well as some generally incorrect equations which fortuituously yielded correct answers only for ED_{50}. An even more serious shortcoming of DRES PROBT was the fact that it issued no warnings for a number of cases where results would be suspect, such as $g > 1$ or heterogeneous data. These shortcomings, together with the fact that the original program had been written for the obsolete IBM 1130 computer in an outmoded programming language (FORTRAN II), prompted us to design a new program that would eliminate the above problems, be cost effective, run on the DRES Honeywell DPS-8 computer and be transportable to different computers.

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[1] In this report, the modified IBM PROBT will be referred to as DRES PROBT.

[2] System/360 Scientific Subroutine Package (360A-CM-03X) Version 3 Programmers Manual, IBM Technical Publications Department, White Plains, N.Y., 44 (1968).

The method of probit analysis used for the new program is also based on the iterative maximum likelihood method of Finney. Robustness for Finney's method is determined primarily by two key items in the program. The first is the method of handling null and 100% responses in the initial iteration. Null responses must be eliminated for the first iteration since they correspond to probits equal to minus infinity. The inclusion of 100% responses can also cause instabilities in the program particularly if several null and 100% responses are present in the data, but it is debatable whether they should be eliminated from the initial iteration or merely weighted differently than the other responses. The second key item is the method of testing for convergence. There are several quantities that can be used to test convergence but which one provides the most accurate answers for the minimum number of iterations is not clear. Since most successful commerical probit analysis programs have their own methods of handling these two operations and they do not provide details of their algorithms, one can only determine how to handle convergence and null/100% responses by trying different approaches. After extensive tests, it was decided to weigh both the null and 100% responses by zero in the first iteration and to use the sensitivity (slope of the regression line) as the test of convergence.

The new PROBIT code is an interactive FORTRAN IV program which yields a complete analysis of probit experiments, or, if desired, a condensed summary of results. The program provides a far more thorough analysis and is markedly less sensitive to the dynamic range of the input data than many personal computer probit programs (Lieberman, 1983) and IBM PROBT.

There are equally sophisticated programs available for mainframe computers, but these were not deemed cost effective for use at DRES, since they are a part of large statistical program packages, such as SAS[3] and S103[4], which

[3] Statistical Analysis System, SAS Institute Inc., SAS Circle, Box 8000, Cary, N.C.

[4] S103 Statistical Package, Engineering and Statistical Research Institute, Agriculture Canada, Ottawa, K1A 0C6

must be purchased or rented in their entirety. Also, these programs cannot normally be modified. This is a significant problem, since it was found that a number of individuals at DRES wanted certain output formats which these codes did not allow. This would be a contining problem as scientists and their tastes change with time. A DRES program, however, could be tailored to suit needs now and be modified later.

An overview of the mainline program is discussed in Section 2.0. Sections 2.1 and 2.2 discuss the pertinent input and output parameters. Section 3 describes the subprograms required by the main program. Results of tests of the program, including a comparison of a number of probit analysis programs are presented in Section 4. The underlying theory behind the program is described in Appendices 1 and 2. A description of operating instructions for the program as implemented on the DRES Honeywell DPS-8/70 and Ordnance Detection Group (ODG) VAX 11/780 is given in Appendix 3. A sample input data file and sample output are given in Appendix 4. Finally, Appendix 5 contains a listing of PROBIT.

2.0 MAIN PROGRAM

Figure 1 shows the hierarchial chart of the probit analysis program. Figure 2 is the flowchart of the main program, PROBIT. The main program controls the input of data, the output of results and the actual iterative maximum likelihood calculation. Once the necessary data have been entered, the iterative procedures begins. It continues until convergence occurs (Appendix 1) or until the number of iterations exceeds a specified value, indicating nonconvergence.

The user has the option of printing intermediate results of the iterative regression at the end of each iteration. This option is controlled by a switch parameter during the input portion of the program, and is particularly useful in analysing the results obtained from data which produced nonconvergence or results which should be viewed with scepticism.

The output comprises some of the best features of a number of probit analysis programs designed for mainframe computers, notably SAS and S103.

2.1 Input

All of the input required for the probit analysis program is "interactive" and is entered directly into the computer, by means of the terminal keyboard. The data is entered in "free" format (excluding the alphanumeric strings), with the numbers separated by a comma or a blank space. The program itself need not be altered for execution; and the user is told what values to enter with default values provided where they might be needed. If the input is entered incorrectly, execution may be interrupted and the values re-entered. Some initial data are printed with the final results. These are shown in Table 1. (In Tables 1 or 2, symbols in brackets refer to the corresponding variables used in Appendices 1 and 2.)

2.2 Output

The output from a sample analysis is given in Appendix 4. Intermediate results have been printed by setting the IYNSW switch to YES. The first three iterations are shown for brevity.

The output for the program PROBIT consists of an initial list of the input data, followed by intermediate results if required for further analysis, and finally the results of the analysis (see Appendices 1 and 2). These include the doses, dose metameters, number of responses, probits, NEDS, standard errors, and weights used for each trial; the means and fiducial limits of the estimated responses, the sensitivity with its standard error; the value of chi-square (χ^2) for the corresponding number of degrees of freedom; the heterogeneity factor; the values of G and T (see below); the effective dose (ED) levels; and finally, the upper and lower fiducial limits corresponding to the given ED tolerance levels. All data are displayed in table form with suitable headings, and the title is printed at the top of each new page. Error messages have also been included where they may be needed. The final output quantities are summarized in Table 2.

Data which may be used to calculate relative potency are printed in a format suitable for direct entry to a program, RPOTC (Appendix 6). The theory behind the program is beyond the scope of this report, but is found in Chenier, 1966 and Finney, 1971.

3.0 FUNCTION SUBPROGRAMS

Four function subprograms (one of which calls two more function subprograms) are required by the main program to transform between NED values and probability of response, and to compute values of the χ^2 and Student-t distributions. The subprograms are briefly described below.

3.1 Name: Function XNED(Q) (Figure 3)

Purpose: The function XNED(Q) is called by the main program to calculate the normal equivalent deviate (NED) value for a probability of no response, Q. XNED(Q) has a maximum error of ±0.0004 over the given range $(0.0 < Q < 1.0)$. When Q is outside of this range, values are set accordingly: i.e., if $Q = 0$, NED = 5.0; if $Q = 1$, NED = -5.0. The transformation used for this function is from Hastings (1955).

Input Parameters: The one input parameter for this function is passed directly from the mainline program.

Q - real; probability of no response

Output Parameters: None (except possible error messages).

3.2 Name: Function RESP(Y) (Figure 4)

Purpose: This function is called from the mainline program to calculate the probability of response, P, given the NED value, Y. RESP(Y) has a maximum error of $\pm 3 \times 10^{-7}$ and uses the transformation from Hastings (1955).

Input Parameters: The only input parameter for the function RESP(Y) is passed from the main program.

Y - real; normal equivalent deviate value (NED)

Output Parameters: None.

3.3 Name: Function PCHISQ(CHISQR, NFREE) (Figure 5)

Purpose: This function is called from the main program, to evaluate the probability of exceeding χ^2, given the estimate of reduced χ^2, CHISQR, and the number of degrees of freedom, NFREE (Bevington, 1969). It should be noted that for NFREE odd and $\chi^2 > 50$, the calculation is only an approximation.

Input Parameters: The following parameters are passed from the mainline program.

CHISQR - real; estimate of reduced χ^2
NFREE - integer; number of degrees of freedom

Output Parameters: None, except possible error messages.

3.4 Name: Function GAMMS(X) (Figure 6)

Purpose: The function GAMMS(X) is called by PCHISQ to evaluate the gamma function for integers and half-integers (Bevington, 1969).

Input Parameters: The only parameter for this function is passed from the function PCHISQ.

X - real; real form of the integer or half-integer argument.

Output Parameters: None.

3.5 Name: Function FACTOR(N) (Figure 7)

Purpose: This function subprogram is called by GAMMS to calculate the factorial function for integers (Bevington, 1969). This is used when the argument is integral, and thus when the gamma function is identical to the factorial function: FACTOR(N) = N!. For N less than 11, this computation is straightforward multiplication, but logarithms are needed for larger values in order to preserve precision.

Input Parameters: The only input parameter used in this function is passed from GAMMS(X).

N - integer; integer argument used for calculations.

Output Parameters: None.

3.6 Name: Function TPROB(FREE,ALPHA) (Figure 8)

Purpose: This function is called from the main program to find the value of 'T' from a Student's-t distribution of FREE degrees of freedom, which is exceeded with probability ALPHA (2 sided test). The T distribution table (Thompson, 1941) is stored in a data file, and is read as input into a 2-dimensional array. The values are then read and interpolation is carried out where necessary to get an accurate value of 'T'. Tests are conducted throughout the program to determine special cases for FREE and ALPHA. If FREE $<$ 1 or ALPHA $<$ 0.5, the program terminates. If FREE $>$ 120 the value of FREE = ∞ is used, and if ALPHA $>$ 0.995 the value of ALPHA = 0.995 is used. Tests are also used to determine if interpolation is necessary, and if so, whether it is needed for either the ALPHA or FREE variables, or both. A simple first order (linear) interpolation is used.

Input Parameters: As well as the two parameters passed from the main program there is the data array read from a data file. Thus, the following are all classed as input:

FREE - real; number of degrees of freedom

ALPHA - real; confidence level of fiducial limits

T - real; data array of 'T' distribution table

Output Parameters: None, except possible error messages.

4.0 TESTS OF THE PROBIT PROGRAM

In order to test how well the new probit analysis program performed, sample data were analysed using the PROBIT, DRES PROBT, SAS and S103 programs. The first two programs are based on modified forms of the iterative maximum likelihood method of Finney (1971). No information is available on the specific algorithms used for SAS and S103, since most commerical statistical packages heavily guard their methods. However, because of the popularity of Finney's method, it is suspected that they too employ a form of it.

4.1 Comparison of "PROBIT" and "DRES PROBT"

The first test compared the DRES programs, PROBIT and DRES PROBT.

The data sets which were used are listed in Table 3. The data sets are typical of those analysed at DRES and provide a mixture of homogeneous and heterogeneous data.

Estimates of representative quantities estimated by both programs are presented in Table 4. Other quantities, such as other ED levels and corresponding fiducial limits, are available from the new program PROBIT but those listed are sufficient to allow a satisfactory comparison of the programs.

Both programs consistently agree on only two quantities, sensitivity and ED_{50} estimates. It is immediately clear that DRES PROBT miscalculates the number of degrees of freedom, ν, since this should be the number of samples in a series minus 2. The reason for the miscalculation is understood, but a discussion of it

is beyond the scope of this report. Also, DRES PROBT does not estimate "g" when data are found to be homogeneous, nor does it estimate other ED values or their fiducial limits.

The two programs disagreed on their estimates of reduced χ^2. This would be expected for the series where DRES PROBT miscalculated ν, but surprisingly occurred even when ν was correct. The estimates of the standard error in the sensitivities agreed in all series except for the first, where the DRES PROBT extimate was 1.96 times larger than that of PROBIT. This can be explained, however, by noting that in the first series, DRES PROBT declared the data to be heterogeneous whereas PROBIT determined it to be homogeneous. Thus, DRES PROBT multiplied the PROBIT estimate of the standard error by the square root of the heterogeneity factor (=1.96). The discrepancy in heterogeneity related to the error in DRES PROBT caused the number of degrees of freedom to be miscalculated.

Finally, PROBIT generally converged much more quickly than DRES PROBT. In 22% (2/9) of the series, convergence required the same number of iterations as DRES PROBT, but in 66% (6/9) of the series, PROBIT converged using on the average 1/3 of the number of iterations of DRES PROBT. In one series, DRES PROBT failed to converge whereas PROBIT succeeded.

4.2 Comparison of "PROBIT", "SAS" and "S103"

PROBIT results were tested against two commerical PROBIT analysis programs, SAS and S103, using data sets listed in Table 5. The data sets included several series with single and multiple null and 100% responses. Such data, which are incompatible with DRES PROBT, provide a severe test of program robustness.

Estimates of representative quantities obtained for PROBIT (Table 6) were very similar to those obtained for S103 and slightly different from those of SAS. In any case, the differences in values form one program to another were not statistically significant. S103 did not have a convergence criterion but rather ran for a fixed number of iterations, in this case 20, which is far more than is normally required. This suggests that SAS may have been one or two iterations

away from true convergence. In 33% (3/9) of the series, PROBIT required one less iteration than SAS and in one series, SAS required one less iteration than PROBIT. The biggest differences between all three programs occurred in the calculation of ED_{95} and the fiducial limits, being the most pronounced for the ED_{95}. This is because fiducial limits are quite sensitive to slight errors in estimation of the regression slope, and because any error in calculating the regression slope is compounded as one estimates quantities progressively further from the mean of the data.

4.3 "PROBIT" Transportability

Finally, to test transportability of the code, the PROBIT source file was transferred on 9 track digital magnetic tape to the ODG Digital Equipment VAX 11/780, recompiled, and relinked. The data sets of Table 3 and 5 were reanalysed and the results were found to be identical to those from the Honeywell computer.

5.0 DISCUSSION AND CONCLUSIONS

Clearly, PROBIT performs much better than the old DRES PROBT program and is comparable to the probit programs contained in the two commerical packages, S103 and SAS. It may, indeed, actually perform slightly better than SAS.

Commerical statistical package programs are provided in an executable image form, which means that they cannot be modified. This can be a major drawback, since output must then be tailored to satisfy a large number of scientists of differing disciplines. The output of the PROBIT program is currently configured to the needs of a much smaller number of DRES scientists with relatively similar interests. Further, it can be modified as needs change.

Finally, commerical statistical packages are exceedingly expensive. Curently, they are rented for upwards of $1000 per month or are purchased for between $10000 and $25000. The development of PROBIT cost approximately $8000.

In light of these facts, the development of the PROBIT program has been a cost effective and worthwhile endeavour.

REFERENCES

Bevington, P.R. (1969). "Data Reduction and Error Analysis for Physical Sciences", McGraw-Hill Book Co.

Chénier, L.-P., Wenner, B.J. and Goldie, D.W. (1962). "A programme for the calculations of probit analysis (Finney) by the Stantec Zebra digital electronic computer". Suffield Technical Note 107. Suffield Experimental Station, Ralston, Alberta. (U)

Chénier, L.-P. (1966). "A programme for the analysis of relative potency (Finney) by the Stantec Zebra digital electronic computer". Suffield Technical Note 103. (U)

Eisenhart, C., Hastay, M.W. and Wallis, W.A. (1947). "Techniques of Statistical Analysis", McGraw-Hill Book Co., pp. 341-352.

Finney, D.J. (1971). "Probit Analysis", Third Edition, Cambridge University Press, London.

Hastings, C. (1955). "Approximations for Digital Computers", Princeton University Press, Princeton, N.J., pp. 201.

Lieberman, H.R. (1983). "Estimating LD50 using the probit technique: A basic computer program", Drug and Chemical Toxicology, 6(1), pp. 111-116.

Thompson, C.M. (1941). "Table of percentage points of the incomplete beta functions", Biometrika 32, 168-181.

APPENDIX 1

ITERATIVE ESTIMATION OF EFFECTIVE DOSE

APPENDIX 1

Iterative Estimation of Effective Dose

A complete discussion of the theory of probit analysis is beyond the scope of this report and may be found in the definitive text of Finney (1971) and Eisenhart et al. (1947). The present technique is a modification of those of a number of authors, primarily Finney (1971). We present here sufficient theory to make the method clear.

The probability that an organism will respond, (e.g., die) if given a dose, x', of a drug can be represented by assuming that:

1. Each organism is characterized by a definite sensitivity, s', (the minimum dose at which it will respond),

2. sensitivities are log-normally distributed and

3. organism responses are uncorrelated.

The justification and validity of these assumptions have been discussed extensively (Finney, 1971), but for most biological experiments, the assumptions appear valid.

Thus if we define

$$s = \ln(s') \tag{1}$$

$$x = \ln(x') \text{ (x is called a "dose metameter")}$$

then the probability density function of s, p(s), is given by:

$$p(s) = \sigma^{-1} (2\pi)^{-1/2} \exp \{-(s-\mu)^2/2\sigma^2\} \tag{2}$$

The proportion of animals that do not respond for an infinite sample, denoted Q(x), is given by

$$Q(x) = \sigma^{-1} (2\pi)^{-1/2} \exp \int_{s=x}^{\infty} \exp \{-(s-\mu)^2/2\sigma^2\} ds \qquad (3)$$

The proportion that responds, called the 'response', for a dose metameter x, is given by

$$P(x) = 1 - Q(x) \qquad (4)$$

In practice, the sample size is not infinite and instead there is a set of trials (i.e. treatment groups) $\{i = 1, 2, \ldots n\}$ in which a given dose metameter, x_i, yields a number of responses, r_i, for n_i organisms. If we can estimate μ and σ from the data, the entire distribution is known and hence the effective dose for any percentile can be calculated.

We define $P_i = r_i/n_i$ and $Q_i = 1 - P_i$. It can be easily shown that P_i and Q_i are samples from a binomial distribution. Q_i is an estimate of $Q(x_i)$ where

$$Q(x_i) = \sigma^{-1} (2\pi)^{-1/2} \int_{s=x_i}^{\infty} \exp \{-(s-\mu)^2/2\sigma^2\} ds$$

$$= (2\pi)^{-1/2} \int_{s=Y(x_i)}^{\infty} \exp \{-s^2/2\} ds \qquad (5)$$

$$\text{where } Y(x_i) = (x_i - \mu)/\sigma \qquad (6)$$

Y in this form is said to be a 'normal equivalent deviate', or 'NED', A probit, Y', is defined as:

$$Y' = Y + 5 \qquad (7)$$

Y can be estimated by y_i where

$$Q_i = (2\pi)^{-1/2} \int_{s=y_i}^{\infty} \exp\{-s^2/2\}\, ds \qquad (8)$$

y_i may be obtained from Q_i by means of tables or, more appropriately for computer usage, by means of a transformation ($y_i = T_1(Q_i)$) such as is found in Hastings (1955). (It should be noted at this point that if the natural response rate, P_0, defined as the fraction of organisms that respond in the absence of stimulus for an infinite population, is significant with respect to the response rates when the stimulus is present, then it is straightforward to show that the estimate of the response due to the stimulus for trial i, denoted P_i' is given by:

$$P_i' = (P_i - P_0)/(1 - P_0) \qquad (9)$$

and $$Q_i = 1 - P_i' \qquad (10)$$

Q_i is then used in equation (8) and subsequent equations.

We thus obtain a set of pairs of data (x_i, y_i) which should be linearly related if the assumptions listed previously are correct, since:

$$Y(x_i) = A_0 + A_1 x_i \qquad (11)$$

where $A_0 = -\mu\sigma^{-1}$

and $A_1 = \sigma^{-1}$

Using equation (11) as a model, the coefficients A_0, A_1 may be estimated by performing a weighted linear least squares regression of y_i to x_i.

Assuming appropriate weights, w_i, for each trial i, are known (we shall return to this point), the estimate of A_1, called the 'sensitivity', is denoted a_1, and it and its estimated variance, $S_{a_1}^2$, are given by:

$$a_1 = S_{xy}{}^2/S_x{}^2 \tag{12}$$

$$S_{a_1}{}^2 = (\hat{\chi}_\nu{}^2 \quad \nu^{-1})/S_x^2 \tag{13}$$

The variance element S_x^2 and covariance element $S_{xy}{}^2$ are given by:

$$S_x{}^2 = (\sum_{i=1}^n n_i w_i)(\sum_{i=1}^n n_i w_i x_i^2) - (\sum_{i=1}^n n_i w_i x_i)^2 \tag{14}$$

$$S_{xy}{}^2 = (\sum_{i=1}^n n_i w_i)(\sum_{i=1}^n n_i w_i x_i y_i) - (\sum_{i=1}^n n_i w_i x_i)(\sum_{i=1}^n n_i w_i y_i) \tag{15}$$

and $\hat{\chi}_\nu{}^2$ is an estimate of the chi-square parameter for the regression (number of degrees of freedom, $\nu = n-2$) given by:

$$\hat{\chi}_\nu{}^2 = S_y{}^2 - a_1 S_{xy}{}^2 \tag{16}$$

where

$$S_y{}^2 = (\sum_{i=1}^n n_i w_i)(\sum_{i=1}^n n_i w_i y_i^2) - (\sum_{i=1}^n n_i w_i y_i)^2 \tag{17}$$

($\hat{\chi}_\nu{}^2 \nu^{-1}$ is called an estimate of the "reduced chisquare")

We also define:

$$\overline{x} = (\sum_{i=1}^n n_i w_i x_i)/(\sum_{i=1}^n n_i w_i) \tag{18}$$

$$\overline{y} = (\sum_{i=1}^n n_i w_i y_i)/(\sum_{i=1}^n n_i w_i) \tag{19}$$

Then we can estimate $Y(x_i)$ by $y(x_i)$

$$y(x_i) = a_1 (x_i - \overline{x}) + \overline{y} \tag{20}$$

The parent probability density function from which y_i is a sample is not actually known. Generally, it is not a normal distribution and thus a least squares estimate of A_1 would not be a maximum likelihood estimate. To a first approximation, this is equivalent to saying that the variance of $y(x_i)$ is a function of $y(x_i)$. Thus the problem can be circumvented by weighting each sample (Bevington, 1969) but the appropriate weights to use, w_i, are not a priori known. To estimate the proper weights, an iterative procedure (given for the kth iteration where iteration number is shown as a bracketted superscript) is used):

1. calculate $a_1^{(k)}$, $S_{a_1}^{2\ (k)}$, $S_x^{2(k)}$, $S_{xy}^{2\ (k)}$, $S_y^{2(k)}$, $\hat{\chi}_\nu^{2(k)}$, $\bar{x}^{(k)}$, $\bar{y}^{(k)}$, $y(x_i)^{(k)}$ using (12) - (20)

2. calculate $P_i^{(k)} = T_2(y(x_i)^{(k)},$ (21)

$$= (2\pi)^{-1/2} \int_{s=-\infty}^{y(x_i)^{(k)}} \exp\{-s^2/2\}\, ds$$

3. calculate $Q_i^{(k)} = 1 - P_i^{(k)}$ (22)

4. calculate $Z_i^{(k)} = (2\pi)^{-1/2} \exp\{-y_i^{(k)}/2\}$ (23)

5. calculate $Y_i^{(k+1)} = y^{(k)}(x_i) + (Q_i^{(k)} - Q_i)/Z_i^{(k)}$ (24)

6. $w_i^{(k+1)} = Z_i^{2(k)}/\{Q_i^{(k)}[(1-P_0)^{-1} - Q_i^{(k)}]\}$ (25)

7. go to 1 for k+1 iteration.

To begin the iteration process, the following are used as initial values:

$$Q_i^{(1)} = Q_i$$

$$w_i^{(1)} = 1$$

$$Y_i^{(1)} = T_1(Q_i^{(1)})$$

The iteration is repeated until convergence occurs or until a maximum number of iterations have been performed. The criterion $\delta = |a_1^{(k)} - a_1^{(k-1)}|$ may be used to test for convergence.

Failure to converge is usually caused by one of two conditions:

1. The data are heterogeneous (see Appendix 2).
2. The experimental design is not adequate, usually because the input data contains several trials with null and/or 100% oberved responses.

The justification for the method is not obvious and is beyond the scope of this report, but it can be shown that convergence is assured and that maximum likelihood estimates of the parameters are obtained, provided that the previously discussed assumptions are valid (Finney, 1971). Reasons for estimating A_0, A_1 instead of σ, μ are are also discussed.

When iteration is terminated, we can determine the effective dose at the λ percentile level or ED_λ; that is the dose at which λ percent of an infinite population of the organisms would respond. The ED_λ, denoted symbolically as x'_λ, is calculated as follows:

$$P_\lambda = \lambda/100 \qquad (26)$$

$$y_\lambda = T_1(1-P_\lambda) \qquad (27)$$

$$x_\lambda = a_1^{-1}(y_\lambda - \bar{y}) + \bar{x} \qquad (28)$$

where a_1, $\bar{y}$, $\bar{x}$, are the values of $a_1^{(k)}$, $\bar{y}^{(k)}$, $\bar{x}^{(k)}$ after the last iteration and

$$ED_\lambda = x'_\lambda = \exp(x_\lambda) \qquad (29)$$

APPENDIX 2

ERROR ANALYSIS

APPENDIX 2

Error Analysis

Error analysis must be carried out after the effective dose estimation in order to determine the following:

1. the uncertainties of the estimated parameters, and
2. the validity of the assumptions concerning the data as discussed in Appendix 1.

As in Appendix 1, only an outline of the error analysis will be given and the interested reader should refer to any standard text on probit analysis (e.g., Finney, 1971) for theroretical justifications and a discussion of limitations.

$\chi_\alpha^2(\nu)$ is defined as the value of a variable from a chi-squared distribution such that

$$\int_{\chi^2 = \chi_\alpha^2(\nu)}^{\infty} P_\nu(\chi^2)\, d\chi^2 = \alpha, \tag{30}$$

where $P_\nu(\chi^2)$ is the probability density function of a chi-square distribution of ν degrees of freedom. $P_\nu(\chi^2)$ may be calculated from an equation or from tables in any standard statistical text.

If $\hat{\chi}_\nu^2 > \chi_\alpha^2(\nu)$ (see (16)), it is said that the data is "heterogenous". A heterogeneity factor, h, is defined as

$$\begin{aligned} h &= \hat{\chi}_\nu^2/\nu \text{ if } \hat{\chi}_\nu^2 > \chi_\alpha^2(\nu) \\ &= 1 \text{ otherwise.} \end{aligned} \tag{31}$$

The significance of the heterogeneity factor is frequently misunderstood. Data will be heterogenous if the iterative regression analysis of Appendix 1 does not correspond to a maximum likelihood estimation. This may be caused by:

1. correlation of response within a trial due to a lack of independence of subjects within the treatment group (This may lead to increased dispersion about the regression line and a large value of $\hat{\chi}^2_\nu$. If this is the case, h can be regarded as a factor by which all weights have been underestimated since for homogeneous data $\hat{\chi}^2_\nu \approx \nu$. The variance and covariances S^2_x, S^2_y, S^2_{xy} can then be multiplied by h.), or

2. an incorrect mathematical model. (One cannot compensate for such deviations within the framework of the analysis.)

It is generally impossible to separate the first type of deviation (random deviation) from the second type (systematic deviation).

The best advice is to treat all data which are found to be heterogeneous with great caution, and never to multiply variances by h as a "cure" for heterogeneity unless one can be sure that systematic deviations do not occur. Inspection of the regression data and line is essential. In the present program, a warning message is issued whenever heterogeneous data occur, but the multiplication of variances by h is still carried out. Frequently it is found that if convergence occurs the data will be homogeneous.

A final check of goodness of fit can be obtained by computing the expected frequence of response, p_i from the final model after regression, for each trial. If a number of expected frequencies (or their complements) are very small, one should suspect any large value of χ^2.

Let $t_\alpha(\nu)$ be a variable from a Student's t distribution (see any standard statistics text) for ν degrees of freedom such that

$$\int_{-t_\alpha(\nu)}^{t_\alpha(\nu)} P(t)dt = 1 - \alpha \tag{32}$$

where P(t) is the probability density function of t. We define a quantity g (the g factor) as

$$g = t_\alpha^2 S_{a_1}{}^2/a_1{}^2 = ht_\alpha{}^2/\ (a_1 S_{xy}{}^2) \tag{33}$$

$$\text{where}\quad t_\alpha^2 = t_\alpha^2(\nu) \qquad h > 1 \tag{34}$$

$$= t_\alpha^2(\infty) \qquad h = 1.$$

Fiducial limits for x_λ (the range of x over which the true x_λ is certain to lie at the α confidence level) is given by:

$$f_\lambda = x_\lambda + \frac{g}{1-g}(x_\lambda - \bar{x}) \pm \left\{ \frac{(1-g)}{\sum_{i=1}^{n} n_i w_i} + \frac{(x_\lambda - \bar{x})^2}{S_x{}^2} \right\}^{1/2} \left\{ \frac{t_\alpha}{a_1(1-g)} \right\} \tag{35}$$

where the plus sign corresponds to the upper limit, $f_{u\lambda}$, and the minus sign corresponds to the lower limit, $f_{l\lambda}$.

The fiducial or Fieller limits on x'_λ, i.e., the ED_λ are then

$$f'_\lambda = \exp\ \{f_\lambda\} \tag{36}$$

It can be readily shown that

$$g = t_\alpha^2\ \nu^{-1}\ (r^{-2} - 1) \tag{37}$$

where r is the correlation coefficient (Bevington, 1969) for the regression. Since $-1 < r < 1$, then $g > 0$.

Clearly if the regression data are highly correlated or anti correlated ($r \approx \pm 1$), g will be approximately zero and the fiducial limits are well defined. If $g > 1$, ie, $r^2 < (\nu t_\alpha^{-2} + 1)^{-1}$ then the lower fiducial limit is greater than the upper, a nonsensical result. Detailed analysis shows that when this occurs, the range of x over which the true x_λ is certain to occur at the α confidence level is outside the range given by the two limits. Values of g for "well behaved" data are typically 0.1 and seldom exceed 0.4 (Finney, 1971). For values of g larger than 0.4, the experimenter should view the experiment with some skepticism.

APPENDIX 3

OPERATING INSTRUCTIONS

APPENDIX 3

Operating Instructions

The probit analysis program PROBIT is currently running on the DRES Honeywell DPS-8 and the ODG Digital Equipment VAX 11/780 computers. Procedures for operating the program on both computers follow.

Procedure for Interactive Use on the Honeywell Computer:

(1) Log on the terminal with the following account number and password: BIOØØ2ØØ,STATS,DRES. Press the RETURN key. Enter N to profile change.

(2) A menu consisting of several statistical analysis options will appear. Find the number corresponding to the probit analysis option (2). Enter the number and press the RETURN key.

(3) User will be prompted with question:
Do you have an input file already created? (Y/N)

(4) If answer to #3 is N, then user is prompted with:
Do you want to create an input file before running PROBIT? (Y/N)

(5) If answer to #4 is N, then PROBIT program will prompt user to input data while the program is running.

(6) If answer to #4 is Y, then a paragraph of steps of explanation detailing how to build a file and the format for the data is described. A sample file is also provided as an example.

(7) If answer to #3 is Y, then user is prompted with:
'Enter file name'
After that entry, PROBIT will run successfully.

(8) Perform interactive probit analysis for a data set. The computer, using simple instructions, asks the user for the appropriate input data. Numbers on a line are separated by a blank or comma. If incorrect information has been entered and the RETURN key has not be pressed, the BACKSPACE key may be used to delete the erroneous data which may then be re-entered. If incorrect information has been entered and the RETURN key has been pressed, the ESC Y key must be pressed an all previous data must be re-entered.

(9) After analysis of each data set, PROBIT will ask if you wish to exit the program. If 'yes' is chosen, the main menu will be returned and you may carry out other analyses or exit from the statistics package.

(10) Afterwards, the output may be picked up from the line printer.

Procedure for the VAX 11/780 Computer:

(1) Log on the terminal under your account.
The terminal should previously be set for 132 columns of output.

(2) If input and output are to be via your terminal type the following:
@ DISK$MRCG1:[JEM.STATS]PROBITTERM

(3) Alternatively, the user can enter the input from and place the output in data files by typing:
@ DISK$MRCG1:[JEM.STATS]PROBITFILE
It is assumed that the data to be entered have already been placed in a file using the EDT editor. The input data format is demonstrated in Appendix 4. You will be prompted for the file name and for an output filename. The output file need not initially exist.

(4) Perform probit analysis for a data set. When using PROBITTERM the interactive process is the same as for the Honeywell computer except that the RUBOUT and CTRL Y keys are used for data correction instead of the BACKSPACE and ESC Y keys respectively.

(5) After analysis of each data set, the computer will ask the user whether he/she wishes to terminate analysis. If 'yes' is chosen, you will be returned to the monitor (DCL) level.

(6) To logoff, type LOG.

APPENDIX 4

SAMPLE INPUT DATA FILE AND SAMPLE OUTPUT OF PROGRAM PROBIT

SAMPLE INPUT DATA FILE :

```
SERIES 9 GROUP 2
4,50
YES
10. 585. 10.
10. 526.5 6.
10. 473.9 2.
10. 426.5 3.
0.95
0.0 0.001
```

SAMPLE PROBIT OUTPUT:

PROBIT ANALYSIS
SERIES 9 GROUP 2

INITIAL INPUT DATA:

GROUP NUMBER	NUMBER OF ANIMALS	DOSE	NUMBER OF RESPONSES
1	10.00	585.0	10.00
2	10.00	526.5	6.00
3	10.00	473.9	2.00

PROBIT ANALYSIS
SERIES 9 GROUP 2

NUMBER OF GROUPS: 4

MAXIMUM LOOP COUNT: 50

OUTPUT OF INTERMEDIATE RESULTS: YES

CONFIDENCE LEVEL OF FIELLER LIMITS: 0.9500

FRACTION OF NATURAL MORTALITY: 0.00000

CONVERGENCE CRITERION: 0.00100

INITIAL CALCULATED VALUES:

GROUP NUMBER	DOSAGES	EMPIRICAL RESPONSES	EMPIRICAL NEDS	WEIGHTS
1	0.63716E+01	1.000	0.50000E+01	0.000
2	0.62663E+01	.6000	0.25293E+00	1.000
3	0.61610E+01	.2000	-0.84146E+00	1.000
4	0.60556E+01	.3000	-0.52400E+00	1.000

PROBIT ANALYSIS
SERIES 9 GROUP 2

INTERMEDIATE RESULTS:

LOOP NUMBER: 1

REGRESSION COEFF.(SLOPE) --B	VARIANCE OF DOSAGES --SXX	VAR. OF PREVIOUS LOOP WORKING NEDS --SYY	COVAR. OF PREVIOUS LOOP WORKING NEDS AND DOSAGES--SXY	MEAN OF DOSAGES --XBAR	MEAN OF PREVIOUS LOOP WORKING NEDS --YBAR	CHISQ
0.36871E+01	0.73948E-02	0.21134E+00	0.27265E-01	0.61610E+01	-0.37084E+00	0.33244E+01

GROUP NUMBER --I	DOSAGES --X(I)	EXPECTED NEDS FROM PROVISIONAL LINE--Y(I)	WORKING NEDS --YNEW(I)	Q FROM REGRESSION --QREG(I)	ORDINATE CORRESPONDING TO Y(I)--Z(I)	WEIGHT CORRESPONDING TO Y(I)--W(I)
1	0.63716E+01	0.40588E+00	0.13379E+01	0.34242E+00	0.36740E+00	0.59947E+00
2	0.62663E+01	0.17402E-01	0.25070E+00	0.49306E+00	0.39888E+00	0.63655E+00
3	0.61610E+01	-0.37068E+00	-0.78801E+00	0.64456E+00	0.37245E+00	0.60550E+00
4	0.60556E+01	-0.75924E+00	-0.50461E+00	0.77615E+00	0.29904E+00	0.51471E+00

LOOP NUMBER: 2

REGRESSION COEFF.(SLOPE) --B	VARIANCE OF DOSAGES --SXX	VAR. OF PREVIOUS LOOP WORKING NEDS --SYY	COVAR. OF PREVIOUS LOOP WORKING NEDS AND DOSAGES--SXY	MEAN OF DOSAGES --XBAR	MEAN OF PREVIOUS LOOP WORKING NEDS --YBAR	CHISQ
0.64133E+01	0.13224E-01	0.67847E+00	0.84808E-01	0.62200E+01	0.95377E-01	0.31709E+01

GROUP NUMBER --I	DOSAGES --X(I)	EXPECTED NEDS FROM PROVISIONAL LINE--Y(I)	WORKING NEDS --YNEW(I)	Q FROM REGRESSION --QREG(I)	ORDINATE CORRESPONDING TO Y(I)--Z(I)	WEIGHT CORRESPONDING TO Y(I)--W(I)
1	0.63716E+01	0.10677E+01	0.17008E+01	0.14282E+00	0.22561E+00	0.41576E+00
2	0.62663E+01	0.39203E+00	0.24997E+00	0.34752E+00	0.36943E+00	0.60191E+00
3	0.61610E+01	-0.28300E+00	-0.77503E+00	0.61141E+00	0.38328E+00	0.61832E+00
4	0.60556E+01	-0.95886E+00	-0.43812E+00	0.83118E+00	0.25192E+00	0.45229E+00

LOOP NUMBER: 3

REGRESSION COEFF.(SLOPE) --B	VARIANCE OF DOSAGES --SXX	VAR. OF PREVIOUS LOOP WORKING NEDS --SYY	COVAR. OF PREVIOUS LOOP WORKING NEDS AND DOSAGES--SXY	MEAN OF DOSAGES --XBAR	MEAN OF PREVIOUS LOOP WORKING NEDS --YBAR	CHISQ
0.70615E+01	0.11985E-01	0.80590E+00	0.84634E-01	0.62104E+01	0.86288E-01	0.43490E+01

PROBIT ANALYSIS
SERIES 9 GROUP 2

FINAL OUTPUT DATA:

** ITERATIVE REGRESSION CONVERGED AFTER 5 ITERATIONS **

GROUP NUMBER	DOSE	DOSAGES (LN OF DOSE)	EMPIRICAL % RESPONSE	MAXIMUM LIKELIHOOD EXPECTED PROBITS	MAXIMUM LIKELIHOOD EXPECTED NEDS	STANDARD ERROR	WEIGHT
1	585.0	0.63716E+01	100.00	0.62478E+01	0.12478E+01	0.41191E+00	0.35381E+00
2	526.5	0.62663E+01	60.00	0.54945E+01	0.49454E+00	0.25682E+00	0.58215E+00
3	473.9	0.61610E+01	20.00	0.47420E+01	-0.25802E+00	0.24311E+00	0.62138E+00
4	426.5	0.60556E+01	30.00	0.39885E+01	-0.10115E+01	0.38617E+00	0.43478E+00

GROUP NUMBER	DOSE	DOSAGES	NUMBER TESTED	NUMBER REACTING: OBSERVED	EXPECTED: MEAN	95.00% FIDUCIAL LIMITS: LOWER	UPPER
1	585.0	0.63716E+01	10.00	10.00	8.94	0.67021E+01	0.98007E+01
2	526.5	0.62663E+01	10.00	6.00	6.90	0.49648E+01	0.84084E+01
3	473.9	0.61610E+01	10.00	2.00	3.98	0.23132E+01	0.58647E+01
4	426.5	0.60556E+01	10.00	3.00	1.56	0.38498E+00	0.39952E+01

PROBIT ANALYSIS
SERIES 9 GROUP 2

THE EQUATION FOR THE REGRESSION LINE IN NEDS IS:
Y = -44.30805 + 7.1498 X

REGRESSION SLOPE (SENSITIVITY) = 7.1498 +OR- 2.0892 (STANDARD ERROR)

CHI SQUARE = 4.7779 FOR 2 DEGREES OF FREEDOM

THE DATA IS HOMOGENEOUS; THE HETEROGENEITY FACTOR IS H = 1.0; G = 0.32801E+00
T = 0.19600E+01 WITH INFINITE DEGREES OF FREEDOM

EXACT FIELLER LIMITS BELOW GIVE THE 95.00% FIDUCIAL LIMITS

ED LEVEL %	EFFECTIVE DOSE	FIELLER LIMITS LOWER	FIELLER LIMITS UPPER
RESPONSE	IN NATURAL LOGARITHMIC SCALE		
1.00	5.87165	0.54136E+01	0.60031E+01
50.00	6.19708	0.61173E+01	0.62680E+01
90.00	6.37635	0.62962E+01	0.66227E+01
95.00	6.42719	0.63323E+01	0.67378E+01
99.00	6.52252	0.63971E+01	0.69568E+01
RESPONSE	IN ORIGINAL SCALE		
1.00	0.35483E+03	0.22444E+03	0.40470E+03
50.00	0.49131E+03	0.45365E+03	0.52741E+03
90.00	0.58778E+03	0.54249E+03	0.75195E+03
95.00	0.61843E+03	0.56248E+03	0.84370E+03
99.00	0.68029E+03	0.60010E+03	0.10502E+04

***** PARAMETERS NECESSARY FOR RELATIVE POTENCY TEST PROGRAM *****

CHISQ	SNW	XBAR	SXX*SNW	SXY*SNW	DFREE	YBAR	SYY*SNW
0.47779E+01	19.92195	6.20617	0.22911	1.63807	2	0.64935E-01	0.16490E+02

APPENDIX 5

SOURCE LISTING OF PROGRAM PROBIT

```
C       **** MAINLINE PROGRAM ****
C
C       ---- A PROBIT ANALYSIS PROGRAM USED MAINLY TO DETERMINE THE ----
C       PROBABILITY THAT AN ANIMAL WILL RESPOND IF GIVEN A CERTAIN
C       EFFECTIVE DOSAGE OF A DRUG.  ALSO USED TO CALCULATE THE REGRESSION
C       SLOPE, PROBITS, HETEROGENEITY FACTOR, AND FIDUCIAL LIMITS FOR THE
C       GIVEN DATA.
C
C
C       **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C       ---- FUNCTION XNED(Q) ----
C
C            CALLED TO CALCULATE THE NED (NORMAL EQUIVALENT DEVIATE) VALUE
C            FOR A PROBABILITY OF NO RESPONSE, Q.
C
C       ---- FUNCTION RESP(Y) ----
C            CALLED TO CALCULATE THE PROBABILITY OF RESPONSE, P, GIVEN THE
C            NED VALUE, Y.
C
C       ---- FUNCTION PCHISQ(CHISQR,NFREE) ----
C
C            CALLED TO EVALUATE THE PROBABILITY FOR EXCEEDING CHI SQUARE,
C            GIVEN THE COMPARISON VALUE OF REDUCED CHI SQUARE (CHISQR) AND
C            THE NUMBER OF DEGREES OF FREEDOM (NFREE).
C
C       ---- FUNCTION TPROB(FREE,ALPHA) ----
C
C            USED TO FIND THE VALUE OF 'T' FROM A T DISTRIBUTION TABLE OF
C            'FREE' DEGREES OF FREEDOM, WHICH IS EXCEEDED WITH PROBABILITY
C            OF 'ALPHA' (2 SIDED TEST).
C
C
C       **** DESCRIPTION OF VARIABLES ****
C
C       ---- INPUT VARIABLES ----
C
C            ID/ ALPHABETIC; IDENTIFICATION TITLE (PRINTED ON EACH PAGE)
C            NT/ INTEGER; NUMBER OF GROUPS
C            MAXCNT/ INTEGER; MAXIMUM LOOP COUNT FOR ITERATIVE REGRESSION
C            IYNSW/ ALPHABETIC; SWITCH FOR OUTPUT OF INTERMEDIATE RESULTS
C                   IY - YES
C                   IN - NO
C            TN/ REAL; NUMBER OF ANIMALS IN THE GROUP
C            XIN/ REAL; DOSE GIVEN IN THE GROUP
C            R/ REAL; NUMBER OF RESPONSES IN THE GROUP
C            ALPHA/ REAL; CONFIDENCE LEVEL OF FIDUCIAL LIMITS
C                   DEFAULT = 0.95
C            C/ REAL; FRACTION OF NATURAL MORTALITY
C               DEFAULT = 0.0
C            DELTA/ REAL; CONVERGENCE CRITERION
C                   DEFAULT = 0.001
C
C       ---- CALCULATED VARIABLES ----
C
C            I,J,K/ INTEGER; LOOP COUNTERS
C            X/ REAL; DOSAGES (NATURAL LOG OF THE DOSE,XIN)
```

```
C          P/ REAL; PROB. OF RESPONSE AT A GIVEN DOSAGE LEVEL
C          Q/ REAL; PROB. OF NO RESPONSE AT A GIVEN DOSAGE LEVEL
C          W/ REAL; CORRECT WEIGHTING COEFF. CORRESPONDING TO Y
C          Y/ REAL; EXPECTED NEDS FROM PROVISIONAL LINE (EMPIRICAL)
C          PLMBDA/ REAL; ARRAY FOR EFFECTIVE DOSE LEVELS
C          BOLD/ REAL; OLD (PREVIOUS) CALCULATED REGRESSION SLOPE
C          SNW,SNWX,SNWY,SNWXX,SNWYY,SNWXY/ REAL; INTERMEDIATE SUMS
C          XBAR/ REAL; MEAN OF THE DOSAGES
C          YBAR/ REAL; MEAN OF THE WORKING NED'S
C          SXX/ REAL; VARIANCE OF THE DOSAGES
C          SYY/ REAL; VARIANCE OF THE WORKING NED'S
C          SXY/ REAL; COVARIANCE OF THE WORKING NED'S AND DOSAGES
C          B/ REAL; CURRENT REGRESSION SLOPE (REGRESSION COEFFICIENT)
C          QREG/ REAL; Q FROM REGRESSION -- CORRESPONDING TO Y
C          Z/ REAL; ORDINATE CORRESPONDING TO Y
C          CHISQ/ REAL; VALUE OF CHI SQUARE
C          NFREE/ INTEGER; NUMBER OF DEGREES OF FREEDOM
C          FREE/ REAL; NUMBER OF DEGREES OF FREEDOM
C          CHISQR/ REAL; REDUCED CHI SQUARE
C          H/ REAL; HETEROGENEITY FACTOR
C                  H = 1.0; HOMOGENEOUS
C                  H < 1.0 OR H > 1.0; HETEROGENOUS
C          T/ REAL; VALUE OF 'T' DISTRIBUTION
C          SIGMAB/ REAL; ERROR IN SLOPE
C          QLMBDA,YLMBDA,XLMBDA,EDLMB/ REAL; TOLERANCE LEVELS OF VALUES
C          G,FACT,FACT1,FACT2,DIV,EX/ REAL; INTERMEDIATE VALUES
C          FUX,FLX/ REAL; UPPER AND LOWER FIDUCIAL LIMITS FOR X (ERRORS)
C          FUED,FLED/ REAL; UPPER AND LOWER FIDUCIAL LIMITS FOR ED
C          YR/ REAL; MAXIMUM LIKELIHOOD EXPECTED PROBITS (NEDS - 5)
C          PLB/ REAL; ED LEVEL (DOSE LEVEL * 100)
C          APA/ REAL; PERCENT CONFIDENCE LEVEL
C          RP/ REAL; EMPIRICAL PERCENTAGE RESPONSE
C          FST/ REAL; FIRST COEFFICIENT OF REGRESSION LINE EQUATION
C          YNEW/ REAL; WORKING NEDS (NORMAL EQUIVALENT DEVIATES)
C          YK/ REAL; MAXIMUM LIKELIHOOD EXPECTED NEDS
C          SIGY/ REAL; STANDARD ERROR
C          FLY/ REAL; LOWER FIDUCIAL LIMITS OF EXPECTED NUMBER REACTING
C          FUL/ REAL; UPPER FIDUCIAL LIMITS OF EXPECTED NUMBER REACTING
C          RS/ REAL; MEAN OF THE EXPECTED NUMBER REACTING
C          DUMMY/ REAL; ARRAY FOR DUMMY VARIABLE
C          SWXY,SWX,SWY/ REAL; INTERMEDIATE VALUES
C
C
C      **** PROGRAMMER / DAWN RIGBY ****
C      **** DATE / 22/06/82 ****
C      **** Updated / John McFee ****
C      **** Date / 26/02/86 ****
C
C
       IMPLICIT REAL*8 (A-H, O-Z)
       DIMENSION TN(100),XIN(100),R(100),ID(50),P(100),Q(100),W(100)
       DIMENSION X(100),Y(100),QREG(100),Z(100),YR(100),YNEW(100)
       DIMENSION QLMBDA(10),YLMBDA(10),XLMBDA(10),PLMBDA(10),EDLMB(10)
       DIMENSION FACT(10),FACT1(10),FACT2(10),FLX(10),FUX(10),FLED(10)
       DIMENSION PLB(10),RP(100),YK(100),FLY(100),FUL(100),SIGY(100)
       DIMENSION DUMMY(100),RS(100),FUED(10)
       DATA IY/'YES '/,IN/'NO  '/
```

```
      data indev/2/,ioutdev/3/,infodev/6/
C
C     ---- INPUT DATA ----
C
      write(infodev,404)
404   FORMAT(1X,'IF AN INCORRECT VALUE IS "ENTERED" AS INPUT, INTERRUPT
     1THE SYSTEM',/X,'IMMEDIATELY BY PRESSING "ESC Y" TWICE.',/X,
     2'BEGIN THE INPUT PROCEDURE FROM THE BEGINNING.')
      write(infodev,1)
1     FORMAT (1X,'TYPE A SUITABLE EXPERIMENT TITLE'/1X,'EXCLUDING DIRECT
     1 MENTION OF PROBIT ANALYSIS.')
      read(indev,2)ID
2     FORMAT(50A1)
      write(infodev,3)
3     FORMAT (1X,'INPUT THE NUMBER OF GROUPS AND THE MAXIMUM LOOP COUNT'
     1/1X,'(IF UNKNOWN, TYPE 50 (DEFAULT = 50));'/1X,'SEPARATE THESE TWO
     2 INTEGERS BY A BLANK OR A COMMA.')
      read(indev,*) NT,MAXCNT
      write(infodev,4)
4     FORMAT(1X,'TYPE EITHER "YES" OR "NO", DEPENDING UPON WHETHER YOU
     1WANT THE'/1X,'INTERMEDIATE RESULTS PRINTED AS OUTPUT OR NOT.')
      read(indev,5)IYNSW
5     FORMAT(A4)
      write(infodev,6)
6     FORMAT(1X,'INPUT THE NUMBER OF ANIMALS, THE DOSE, AND THE NUMBER
     1OF'/1X,'RESPONSES FOR EACH GROUP, ONE TRIAL PER LINE.'/1X,'THESE
     2MUST BE "REAL" NUMBERS, SEPARATED BY A BLANK OR A COMMA.')
      read(indev,*)(TN(I),XIN(I),R(I), I=1,NT)
      write(infodev,7)
7     FORMAT(1X,'INPUT THE CONFIDENCE LEVEL OF THE FIELLER LIMITS'/1X, '
     1(DEFAULT=.95; REFER TO THE ABOVE "MAX. LOOP COUNT" EXPLANATION',/X
     2,'DEFAULT).  THIS MUST BE A "REAL" NUMBER.')
      read(indev,*) ALPHA
      write(infodev,8)
8     FORMAT(1X,'INPUT THE FRACTION OF NATURAL MORTALITY (DEFAULT=0.)'/
     11X,'AND THE CONVERGENCE CRITERION (DEFAULT=.001).'/1X,'THESE MUST
     2BOTH BE "REAL" NUMBERS, SEPARATED BY A BLANK OR A COMMA.')
      read(indev,*) C,DELTA
C
C     ---- OUTPUT OF THE INITIAL DATA ----
C
      write(ioutdev,9 )ID
9     FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
      write(ioutdev,10)
10    FORMAT(1X,//,21X,'INITIAL INPUT DATA:')
      write(ioutdev,11)
11    FORMAT(1X, //,15X,'GROUP NUMBER',9X,'NUMBER OF ANIMALS',9X,
     1'DOSE',9X,'NUMBER OF RESPONSES',/)
      IF(NT.LE.50)GO TO 12
      DO 13  I=1,50
      write(ioutdev,14)I,TN(I),XIN(I),R(I)
13    CONTINUE
      write(ioutdev,9 )ID
      write(ioutdev,11)
      DO 15  I=51,NT
      write(ioutdev,14)I,TN(I),XIN(I),R(I)
15    CONTINUE
```

```
      GO TO 16
 12   DO 17 I=1,NT
      write(ioutdev,14)I,TN(I),XIN(I),R(I)
 14   FORMAT(18X,I4,19X,F7.2,12X,G9.4E2,15X,F7.2)
 17   CONTINUE
 16   write(ioutdev,9)ID
      write(ioutdev,18) NT,MAXCNT,IYNSW
 18   FORMAT(1X,//,12X,'NUMBER OF GROUPS:',I4,//,12X,'MAXIMUM LOOP COUNT
     1:',I4,//,12X,'OUTPUT OF INTERMEDIATE RESULTS: ',A4)
      write(ioutdev,19) ALPHA,C,DELTA
 19   FORMAT(1X,/,12X,'CONFIDENCE LEVEL OF FIELLER LIMITS:',F8.4,//,
     112X,'FRACTION OF NATURAL MORTALITY:',F8.5//12X,'CONVERGENCE CRITER
     2ION:',F8.5)
C
C     ---- INITIAL DATA VALUES ----
C          ASSUME SENSITIVITIES ARE LOG NORMALLY DISTRIBUTED
C
      write(ioutdev,20 )
 20   FORMAT(1X//////21X,'INITIAL CALCULATED VALUES:')
      write(ioutdev,21 )
 21   FORMAT(1X//10X,'GROUP NUMBER',9X,'DOSAGES',9X,'EMPIRICAL RESPONSES
     1',9X,'EMPIRICAL NEDS',9X,'WEIGHTS',/)
      DO 22 I=1,NT
      X(I)=DLOG(XIN(I))
      P(I)=R(I)/TN(I)
      P(I)=(P(I)-C)/(1.0-C)
      Q(I)=1.0-P(I)
      W(I)=1.0
      IF((P(I).EQ.0.0).or.(q(I).eq.0.0)) W(I)=0.0
      Y(I)=XNED(Q(I))
      write(ioutdev,23 )I,X(I),P(I),Y(I),W(I)
 23   FORMAT(14X,I4,12X,E12.5,10X,G9.4E2,16X,E12.5,11X,F7.3)
 22   CONTINUE
      BOLD=1.D+30
      KLMBDA = 5
      PLMBDA(1)=0.01
      PLMBDA(2)=0.50
      PLMBDA(3)=0.90
      PLMBDA(4)=0.95
      PLMBDA(5)=0.99
C
C     ---- REGRESSION LOOP ----
C
C       -- FORM SUMS --
C
      IF(IYNSW.EQ.IN) GO TO 24
      write(ioutdev,25)ID
 25   FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
      write(ioutdev,26)
 26   FORMAT(1X,//,21X,'INTERMEDIATE RESULTS:')
 24   DO 27 J=1,MAXCNT
      SNW=0.
      SNWX=0.
      SNWY=0.
      SNWXX=0.
      SNWYY=0.
      SNWXY=0.
```

```
      DO 28 I=1,NT
      SNW=SNW +TN(I) * W(I)
      SNWX=SNWX +TN(I) * W(I) * X(I)
      SNWY=SNWY +TN(I) * W(I) * Y(I)
      SNWXX=SNWXX +TN(I) * W(I) * X(I)**2
      SNWYY=SNWYY +TN(I) * W(I) * Y(I)**2
      SNWXY=SNWXY +TN(I) * W(I) * X(I) * Y(I)
28    CONTINUE
C
C       -- CALCULATE STATISTICS OF DATA --
C
      XBAR=SNWX/SNW
      YBAR=SNWY/SNW
      SXX=SNWXX/SNW - XBAR**2
      SYY=SNWYY/SNW - YBAR**2
      SXY=SNWXY/SNW - XBAR*YBAR
      IF(SXX-0.0)29,30,29
30    write(ioutdev,31)
31    FORMAT('1',1X,'DOSES HAVE ZERO VARIANCE--REGRESSION IMPOSSIBLE!')
      GO TO 32
29    B=SXY/SXX
      CHISQ= (SYY - B*SXY) * SNW
      DO 33 I=1,NT
      Y(I)=B * (X(I) - XBAR) + YBAR
      IF(Y(I).GT. 5.0) Y(I) = 5.0
      IF(Y(I).LT. -5.0) Y(I) = -5.0
      QREG(I) = 1.0 - RESP(Y(I))
      EX=(-(Y(I)**2)/2.)
      Z(I)=(DEXP(EX))/DSQRT(2.*3.1415926535D0)
      YNEW(I)=Y(I)+(QREG(I)- Q(I))/Z(I)
      DIV = (QREG(I) * ((1./(1.- C)) - QREG(I)))
      IF(DABS(DIV).LT.1.00D-10)GO TO 34
      W(I)=(Z(I)**2)/(DIV)
      GO TO 33
34    W(I)=0.0
33    CONTINUE
      IF(IYNSW.EQ.IN) GO TO 35
      GO TO 36
35    DO 37  I=1,NT
      YK(I) = Y(I)
      Y(I) = YNEW(I)
37    CONTINUE
      IF(J-MAXCNT)38,38,39
39    write(ioutdev,40)
40    FORMAT('1',1X,'WARNING -- REGRESSION MAY NOT BE CONVERGENT')
      GO TO 41
38    IF(DELTA - DABS(B-BOLD))42,43,43
42    BOLD = B
27    CONTINUE
43    GO TO 41
C
C     ---- OPTIONAL OUTPUT OF INTERMEDIATE RESULTS ----
C
36    write(ioutdev,44)J
44    FORMAT(1X,///,2X,'LOOP NUMBER:',I4)
      write(ioutdev,45)
45    FORMAT(1X//4X,'REGRESSION',6X,'VARIANCE OF',6X,'VAR. OF PREVIOUS',
```

```
     16X,'COVAR. OF PREVIOUS',6X,'MEAN OF',6X,'MEAN OF PREVIOUS',6X,
     2'CHISQ'/4X,'COEFF.(SLOPE)',3X,'DOSAGES',10X,'LOOP WORKING NEDS',
     35X,'LOOP WORKING NEDS',7X,'DOSAGES',6X,'LOOP WORKING NEDS'/4X,
     4'--B',13X,'--SXX',12X,'--SYY',17X,'AND DOSAGES--SXY',8X,'--XBAR',
     57X,'--YBAR',/)
      write(ioutdev,46)B,SXX,SYY,SXY,XBAR,YBAR,CHISQ
46    FORMAT(4X,E12.5,4X,E12.5,5X,E12.5,12X,E12.5,7X,E12.5,5X,E12.5,6X,
     1E12.5)
      write(ioutdev,47 )
47    FORMAT(1X///4X,'GROUP',11X,'DOSAGES',10X,'EXPECTED NEDS',9X,'WORKI
     1NG',17X,'Q FROM',7X,'ORDINATE',9X,'WEIGHT'/4X,'NUMBER',10X,'--X(I)
     2',11X,'FROM PROVISIONAL',6X,'NEDS',18X,'REGRESSION',5X,'CORRESPOND
     3ING',4X,'CORRESPONDING'/4X,'--I',30X,'LINE--Y(I)',12X,'--YNEW(I)',
     413X,'--QREG(I)',6X,'TO Y(I)--Z(I)',4X,'TO Y(I)--W(I)'/)
      DO 48 I=1,NT
      write(ioutdev,49 )I,X(I),Y(I),YNEW(I),QREG(I),Z(I),W(I)
49    FORMAT(4X,I4,12X,E12.5,5X,E12.5,12X,E12.5,7X,E12.5,5X,E12.5,6X,
     1E12.5)
48    CONTINUE
      GO TO 35
C
C     ---- FURTHER CALCULATIONS ----
C
41    NFREE = NT - 2
      FREE = NFREE
      CHISQR = CHISQ/FREE
      IF(PCHISQ(CHISQR,NFREE).GE.(1.-ALPHA))GO TO 51
      H=CHISQR
      T = TPROB(FREE,ALPHA)
      GO TO 52
51    H = 1.0
      T = TPROB(900.,ALPHA)
52    SIGMAB =DSQRT(H/(SXX*SNW))
      G =(H * T**2)/(B**2 * SXX * SNW)
      DO 105 I=1,NT
      SIGY(I) = DSQRT((H/SNW) + (H*(X(I)-XBAR)**2/(SXX * SNW)))
      FUL(I) = YK(I) + T * SIGY(I)
      FLY(I) = YK(I) - T * SIGY(I)
      DUMMY(I) = 0.0
105   CONTINUE
      DO 53 K=1,KLMBDA
      QLMBDA(K)=1.- PLMBDA(K)
      YLMBDA(K)=XNED(QLMBDA(K))
      XLMBDA(K)= ((YLMBDA(K)-YBAR)/B)+XBAR
      EDLMB(K)=DEXP(XLMBDA(K))
      IF(G.GT.1.0) GO TO 53
C
C     ---- FIELLER LIMITS (ERRORS IN ED) ----
C
      FACT(K)=((H*(1.-G))/SNW)+(H*(XLMBDA(K)-XBAR)**2)/(SXX*SNW)
      FACT1(K)=DSQRT(FACT(K))* (T/(B*(1.-G)))
      FACT2(K)=XLMBDA(K)+(G/(1.-G))*(XLMBDA(K)-XBAR)
      FLX(K)=FACT2(K)-FACT1(K)
      FUX(K)=FACT2(K)+FACT1(K)
      FLED(K)=DEXP(FLX(K))
      FUED(K)=DEXP(FUX(K))
53    CONTINUE
```

```
      APA = ALPHA * 100.
C
C     ---- OUTPUT OF FINAL RESULTS ----
C
      write(ioutdev,55)ID
55    FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
      write(ioutdev,56)
56    FORMAT(1X,// ,21X,'FINAL OUTPUT DATA:')
      IF(MAXCNT-J)57,58,58
57    write(ioutdev,59)MAXCNT
59    FORMAT(1X, // ,20X, ' !! WARNING -- ITERATIVE REGRESSION FAILED TO
     1 CONVERGE AFTER ',I3,' ITERATIONS'/22X,'- RESULTS FOLLOWING MAY BE
     2 SUSPECT !! ')
      GO TO 60
58    write(ioutdev,61)J-1
61    FORMAT(1X, // ,20X, ' ** ITERATIVE REGRESSION CONVERGED AFTER ',I3
     1,'  ITERATIONS ** ')
60    write(ioutdev,62)
62    FORMAT(1X,////,6X,'GROUP',6X,'DOSE',6X,'DOSAGES',6X,'EMPIRICAL',6X
     1,'MAXIMUM LIKELIHOOD',6X,'MAXIMUM LIKELIHOOD',6X,'STANDARD',6X,
     2'WEIGHT')
      write(ioutdev,63)
63    FORMAT(6X,'NUMBER',15X,'(LN OF',7X,'% RESPONSE',5X,'EXPECTED PROBI
     1TS',8X,'EXPECTED NEDS',11X,'ERROR'/27X,'DOSE)'//)
      IF(NT.LE.50)GO TO 64
      DO 65  I=1,50
      YR(I)=YK(I) + 5.
      RP(I)=P(I)*100.0
      write(ioutdev,67)I,XIN(I),X(I),RP(I),YR(I),YK(I),SIGY(I),W(I)
65    CONTINUE
      write(ioutdev,99)APA
99    FORMAT(1X/////,6X,'GROUP',6X,'DOSE',6X,'DOSAGES',6X,'NUMBER TESTED
     1',6X,'-----------------------NUMBER REACTING--------------------
     2----'/6X,'NUMBER',52X,'OBSERVED',6X,'------------------EXPECTED--
     3----------------'/80X,'MEAN',6X,'--',F6.2,'% FIDUCIAL LIMITS------
     4--'/96X,'LOWER',11X,'UPPER'//)
      DO 101 I=1,50
      RS(I)=RESP(YK(I)) * TN(I)
      FLY(I)=RESP(FLY(I)) * TN(I)
      FUL(I)=RESP(FUL(I)) * TN(I)
      write(ioutdev,100)I,XIN(I),X(I),TN(I),R(I),RS(I),FLY(I),FUL(I)
100   FORMAT(7X,I3,5X,G9.4E2,2X,E12.5,6X,F7.2,14X,F7.2,8X,F7.2,6X,E12.5,
     15X,E12.5)
101   CONTINUE
      write(ioutdev,55)ID
      write(ioutdev,62)
      write(ioutdev,63)
      DO 66  I=51,NT
      YR(I)=YK(I) + 5.
      RP(I)=P(I)*100.0
      write(ioutdev,67)I,XIN(I),X(I),RP(I),YR(I),YK(I),SIGY(I),W(I)
66    CONTINUE
      write(ioutdev,99)APA
      DO 102 I=51,NT
      RS(I) = RESP(YK(I)) * TN(I)
      FLY(I)=RESP(FLY(I)) * TN(I)
      FUL(I)=RESP(FUL(I)) * TN(I)
```

```
      write(ioutdev,100)I,XIN(I),X(I),TN(I),R(I),RS(I),FLY(I),FUL(I)
102   CONTINUE
      GO TO 68
64    DO 69 I=1,NT
      YR(I)=YK(I) +5.
      RP(I)=P(I)*100.0
      write(ioutdev,67)I,XIN(I),X(I),RP(I),YR(I),YK(I),SIGY(I),W(I)
67    FORMAT(7X,I3,5X,G9.4E2,2X,E12.5,3X,F7.2,10X,E12.5,12X,E12.5,7X,
     1E12.5,3X,E12.5)
69    CONTINUE
      write(ioutdev,99)APA
      DO 103 I=1,NT
      RS(I)=RESP(YK(I)) * TN(I)
      FLY(I)=RESP(FLY(I)) * TN(I)
      FUL(I)=RESP(FUL(I)) * TN(I)
      write(ioutdev,100)I,XIN(I),X(I),TN(I),R(I),RS(I),FLY(I),FUL(I)
103   CONTINUE
68    write(ioutdev,70)ID
70    FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
      FST=YBAR - B * XBAR
      write(ioutdev,71 )FST,B
71    FORMAT(1X,///,22X,'THE EQUATION FOR THE REGRESSION LINE IN NEDS IS
     1:'/31X,'Y = ',G14.7E2,' +',G12.5E2,' X')
      write(ioutdev,72)B,SIGMAB
72    FORMAT(1X, / ,22X,'REGRESSION SLOPE (SENSITIVITY) = ',G12.5E2,
     1' +OR- ', G12.5E2,' (STANDARD ERROR)')
      write(ioutdev,73)CHISQ,NFREE
73    FORMAT(1X,/,22X,'CHI SQUARE =',G12.5E2,'  FOR',I4,'  DEGREES OF FR
     1EEDOM')
      IF(PCHISQ(CHISQR,NFREE).GE.(1.-ALPHA))GO TO 74
      H=CHISQ/FREE
      GO TO 75
74    H=1.0
75    IF(H.EQ.1.0)GO TO 76
      write(ioutdev,77)H,G,T,NFREE
77    FORMAT(1X,/,22X,'!!!!! WARNING --- THE DATA IS HETEROGENOUS:  THE
     1HETEROGENEITY FACTOR IS H = ',E12.5,' !!!!!'/22X,'!!!!! G =',E12.5
     2,';  T =',E12.5,' WITH',I4,' DEGREES OF FREEDOM. !!!!!'/22X,'!!!!!
     3 "TREAT PROBIT RESULTS WITH EXTREME CAUTION" !!!!!')
      GO TO 78
76    write(ioutdev,79)G,T
79    FORMAT(1X,/,22X,'THE DATA IS HOMOGENEOUS; THE HETEROGENEITY FACTOR
     1 IS H = 1.0;  G =',E12.5,/31X,'T =',E12.5,' WITH INFINITE DEGREES
     2OF FREEDOM')
78    IF(G.LE.1.0) GO TO 300
      write(ioutdev,301)
301   FORMAT(//22X,'!!!!! WARNING -- G > 1.0; THE FIELLER LIMITS ARE OF
     1NO USE AND HENCE NOT PRINTED !!!!!'/22X,'!!!!! SEE FINNEY, PAGE 79
     2 !!!!!')
300   write(ioutdev,80)APA
80    FORMAT(/////11X,'EXACT FIELLER LIMITS BELOW GIVE THE ',F6.2,'% FID
     1UCIAL LIMITS')
      write(ioutdev,81)
81    FORMAT(//11X,'------------------------------------------------
     1-----')
      write(ioutdev,82)
82    FORMAT(//13X,'ED',10X,'EFFECTIVE',8X,'------FIELLER LIMITS------'/
```

```
     111X,'LEVEL %',7X,'DOSE',16X,'LOWER',10X,'UPPER')
      write(ioutdev,83)
83    FORMAT(//11X,'RESPONSE',6X,'------IN NATURAL LOGARITHMIC SCALE----
     1--')
      DO 84 K =1,KLMBDA
      PLB(K) = PLMBDA(K) * 100.
      IF(G.LE.1.0) GO TO 302
      write(ioutdev,303) PLB(K),XLMBDA(K)
303   FORMAT(12X,F7.2,8X,F8.5)
      GO TO 84
302   write(ioutdev,85) PLB(K),XLMBDA(K),FLX(K),FUX(K)
85    FORMAT(12X,F7.2,8X,F8.5,9X,E12.5,5X,E12.5)
84    CONTINUE
      write(ioutdev,86)
86    FORMAT(/11X,'RESPONSE',6X,'-----------IN ORIGINAL SCALE-----------
     1-')
      DO 87 K=1,KLMBDA
      PLB(K) = PLMBDA(K) * 100.
      IF(G.LE.1.0) GO TO 304
      write(ioutdev,305) PLB(K),EDLMB(K)
305   FORMAT(12X,F7.2,8X,F8.3)
      GO TO 87
304   write(ioutdev,88) PLB(K),EDLMB(K),FLED(K),FUED(K)
88    FORMAT(12X,F7.2,8X,E12.5,9X,E12.5,5X,E12.5)
87    CONTINUE
      write(ioutdev,81)
      SWXY = SNW * SXY
      SWX = SNW * SXX
      SWY = SNW * SYY
      write(ioutdev,389)
389   FORMAT(/////11X,'***** PARAMETERS NECESSARY FOR RELATIVE POTENCY T
     1EST PROGRAM *****'///13X,'CHISQ',9X,'SNW',10X,'XBAR',7X,'SXX*SNW',
     26X,'SXY*SNW',8X,'DFREE',8X,'YBAR',7X,'SYY*SNW')
      write(ioutdev,400) CHISQ,SNW,XBAR,SWX,SWXY,NFREE,YBAR,SWY
400   FORMAT(/10X,E11.5,3X,F10.5,3X,F10.5,3X,F10.5,3X,F10.5,7X,I4,5X,
     1E11.5,3X,E11.5)
32    STOP
      END
```

```
C
C
C      **** FUNCTION XNED ****
C
C      ---- THIS FUNCTION CALCULATES THE NORMAL EQUIVALENT DEVIATE ----
C           (NED) VALUE FOR A PROBABILITY OF NO RESPONSE, Q.  IT ASSUMES
C           THAT NED(Q) HAS A MAXIMUM ERROR OF + OR -.0004 OVER THE GIVEN
C            RANGE ( MOST LIKELY, 0 < Q < OR = .5 ).  THE TRANSFORM USED
C           IS FROM "APPROXIMATIONS FOR DIGITAL COMPUTERS" BY HASTINGS, P
C           RINCETON UNIVERSITY PRESS, PRINCETON, NJ., 1955.
C
C
C      **** USAGE ****
C
C      ---- RESULT = XNED(Q) ----
C
C
C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C      ---- NONE ----
C
C
C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
C
C      ---- PARAMETERS PASSED FROM THE MAINLINE ----
C
C           Q/ REAL; PROBABILITY OF NO RESPONSE ( OF SURVIVAL)
C
C      ---- VARIABLES ----
C
C           ETA/ REAL; INTERMEDIATE VALUE
C           A0,A1,A2,B1,B2,B3/ REAL; CONSTANTS
C
C
C      **** PROGRAMMER / DAWN RIGBY ****
C      **** DATE / 22/06/82 ****
C
C
       FUNCTION XNED(Q)
       IMPLICIT REAL*8 (A-H, O-Z)
       IF(Q.NE.1.0)GO TO 18
C
C      ---- IF Q IS EQUAL TO 1.0 ----
C
       XNED = -5.0
       GO TO 14
18     IF(Q-.5)2,2,4
2      IF(Q-0.0)6,7,8
C
C      ---- IF Q IS LESS THAN OR EQUAL TO 0.0 ----
C
6      write(ioutdev,10)
10     FORMAT('1',1X, 'SUBROUTINE XNED--'/1X,'NED VALUE IS NOT DEFINED;
      1Q<0.0')
       GO TO 13
7      XNED = 5.0
       GO TO 14
```

```
C
C       ---- IF Q IS GREATER THAN 0.5 ----
C
4       ETA =DSQRT(-2.* DLOG(1.0 - Q))
        GO TO 12
C
C       ---- IF Q IS BETWEEN 0.0 AND 0.5 ----
C
8       ETA =DSQRT(-2.* DLOG(Q))
12      A0 = 2.515517
        A1 = 0.802853
        A2 = 0.010328
        B1 = 1.432788
        B2 = 0.189269
        B3 = 0.001308
        XNED= ETA-((A0+A1*ETA+A2*ETA**2)/(1.+B1*ETA+B2*ETA**2+B3*ETA**3))
        IF(Q - .5)14,14,16
C
C       ---- IF Q IS GREATER THAN 0.5 ----
C
16      XNED = -XNED
        GO TO 14
13      STOP
14      RETURN
        END
```

```
C
C
C     **** FUNCTION RESP ****
C
C     ---- THIS FUNCTION IS USED TO CALCULATE THE PROBABILITY OF ----
C          RESPONSE, P, GIVEN THE NED VALUE, Y.  RESP(Y) HAS A MAXIMUM
C          ERROR OF + OR - 3.D-7 AND USES THE TRANSFORMATION FROM
C          "APPROXIMATIONS FOR DIGITAL COMPUTERS" BY C. HASTINGS,
C          PRINCETON UNIVERSITY PRESS, PRINCETON, NJ., 1955.
C
C
C     **** USAGE ****
C
C     ---- RESULT = RESP(Y) ----
C
C
C     **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C     ---- NONE ----
C
C
C     **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
C
C     ---- PARAMETERS PASSED FROM THE MAINLINE ----
C
C          Y/ REAL; NORMAL EQUIVALENT DEVIATE (NED) VALUE
C
C     ---- VARIABLES ----
C
C          X,RES/ REAL; INTERMEDIATE VALUES
C          A1,A2,A3,A4,A5,A6/ REAL; CONSTANTS
C          DENOM/ REAL; DENOMINATOR OF THE EQUATION
C
C
C     **** PROGRAMMER / DAWN RIGBY ****
C     **** DATE / 22/06/82 ****
C
C
      FUNCTION RESP(Y)
      IMPLICIT REAL*8(A-H, O-Z)
      X =DABS(Y) /DSQRT(2.0D0)
      A1 = 7.05230784D-2
      A2 = 4.22820123D-2
      A3 = 9.2705272D-3
      A4 = 1.520143D-4
      A5 = 2.765672D-4
      A6 = 4.30638D-5
      DENOM= 1.+ A1*X + A2*X**2 + A3*X**3 + A4*X**4 + A5*X**5 + A6*X**6
      IF(DENOM.LT.4.869675D+4)GO TO 5
      RES = 0.
      GO TO 3
    5 DENOM = DENOM**16
      RES = .5/DENOM
    3 IF(Y-0.)2,2,4
    2 RESP = RES
      GO TO 6
    4 RESP = 1.- RES
```

```
0058    6     RETURN
0059          END
```

```
C
C
C     **** FUNCTION PCHISQ ****
C
C     ---- CALLED TO EVALUATE THE PROBABILITY FOR EXCEEDING CHI ----
C          SQUARE, GIVEN THE COMPARISON VALUE OF REDUCED CHI SQUARE
C          (CHISQR) AND THE NUMBER OF DEGREES OF FREEDOM (NFREE).  THE
C          CALCULATION IS ONLY AN APPROXIMATION FOR NFREE ODD AND CHI
C          SQUARE GREATER THAN 50.
C
C
C     **** USAGE ****
C
C     ---- RESULT = PCHISQ(CHISQR,NFREE) ----
C
C
C     **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C     ---- FUNCTION GAMMS(X) ----
C
C          CALCULATES THE GAMMA FUNCTION FOR INTEGERS AND HALF-INTEGERS
C
C
C     **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
C
C     ---- PARAMETERS PASSED FROM THE MAINLINE ----
C
C          CHISQR/ REAL; COMPARISON VALUE OF REDUCED CHI SQUARE
C          NFREE/ INTEGER; NUMBER OF DEGREES OF FREEDOM
C
C     ---- VARIABLES ----
C
C          Z, TERM, SUM, PWR/ REAL; INTERMEDIATE VALUES
C          NEVEN/ INTEGER; INTERMEDIATE VALUE
C          FREE / REAL; NUMBER OF DEGREES OF FREEDOM
C          I/ INTEGER; LOOP COUNTER
C          FI/ REAL; LOOP COUNTER
C          IMAX/ INTEGER; MAXIMUM LOOP COUNT
C
C
C     **** PROGRAMMER / DAWN RIGBY ****
C     **** DATE / 22/06/82 ****
C
C
      FUNCTION PCHISQ(CHISQR,NFREE)
      IMPLICIT REAL*8(A-H, O-Z)
      IF(NFREE)12,12,14
12    write(ioutdev,11)
11    FORMAT(3X,'SUBROUTINE RESP --')
      write(ioutdev,13)
13    FORMAT(3X,'** ERROR --- NFREE (DEGREES OF FREEDOM) IS LESS THAN 1;
     1 STOP **')
      GO TO 59
14    FREE = NFREE
      Z= CHISQR* FREE/2.
      NEVEN= 2 * (NFREE/2)
      IF(NFREE - NEVEN)21,21,41
```

```
C
C     ---- NUMBER OF DEGREES OF FREEDOM IS EVEN ----
C
21    IMAX = NFREE/2
      TERM = 1.
      SUM = 0.
      DO 34 I=1,IMAX
      FI=I
      SUM= SUM + TERM
34    TERM = TERM * Z/FI
      PCHISQ = SUM* DEXP(-Z)
      GO TO 60
C
C     ---- NUMBER OF DEGREES OF FREEDOM IS ODD ----
C
41    IF(Z-25.)44,44,42
42    Z= CHISQR* (FREE-1.)/2.
      GO TO 21
44    PWR = FREE/2.
      TERM = 1.
      SUM = TERM/PWR
      DO 56 I=1,1000
      FI=I
      TERM = -TERM * Z/FI
      SUM = SUM + TERM/(PWR + FI)
      IF(DABS(TERM/SUM)-.00001)57,57,56
56    CONTINUE
57    PCHISQ = 1.0 - (Z**PWR) * SUM/GAMMS(PWR)
      GO TO 60
59    STOP
60    RETURN
      END
```

```
C
C
C     **** FUNCTION GAMMS ****
C
C     ---- USED TO CALCULATE THE GAMMA FUNCTION FOR INTEGERS AND ----
C          HALF-INTEGERS
C
C
C     **** USAGE ****
C
C     ---- RESULT = GAMMS(X) ----
C
C
C     **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C     ---- FUNCTION FACTOR(N) ----
C
C          CALCULATES N FACTORIAL FOR INTEGERS
C
C
C     **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
C
C     ---- PARAMETERS PASSED FROM THE FUNCTION PCHISQ ----
C
C          X/ REAL; REAL FORM OF INTEGER OR HALF-INTEGER ARGUMENT
C
C     ---- VARIABLES ----
C
C          N/ INTEGER; INTERMEDIATE VALUE
C          XN,SUM/ REAL; INTERMEDIATE VALUES
C          PROD/ REAL; CONSTANT
C          I/ INTEGER; LOOP COUNTER
C          FI/ REAL; LOOP COUNTER
C
C
C     **** PROGRAMMER / DAWN RIGBY ****
C     **** DATE / 22/06/82 ****
C
C
      FUNCTION GAMMS(X)
      IMPLICIT REAL*8(A-H, O-Z)
C
C     ---- INTEGERIZE ARGUMENT ----
C
      N=X-.25
      XN=N
      IF(X-XN-.75)31,31,21
C
C     ---- ARGUMENT IS INTEGER ----
C
 21   GAMMS = FACTOR(N)
      GO TO 60
C
C     ---- ARGUMENT IS HALF-INTEGER ----
C
 31   PROD = 1.77245385
      IF(N)44,44,33
```

```
33      IF(N-10)41,41,51
41      DO 43 I=1,N
        FI = I
43      PROD = PROD * (FI-.5)
44      GAMMS = PROD
        GO TO 60
51      SUM = 0.
        DO 54 I=11,N
        FI = I
54      SUM = SUM +DLOG(FI-.5)
        GAMMS = PROD * 639383.8623 *DEXP(SUM)
60      RETURN
        END
```

```
C
C
C     **** FUNCTION FACTOR ****
C
C     ---- CALLED TO CALCULATE THE FACTORIAL FUNCTION FOR INTEGERS ----
C
C
C     **** USAGE ****
C
C     ---- RESULT = FACTOR(N) ----
C
C
C     **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C     ---- NONE ----
C
C
C     **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
C
C     ---- PARAMTERS PASSED FROM THE FUNCTION GAMMS ----
C
C          N/ INTEGER; INTEGER ARGUMENT FOR CALCULATIONS
C
C     ---- VARIABLES ----
C
C          I/ INTEGER; LOOP COUNTER
C          FI/ REAL; LOOP COUNTER
C          SUM/ REAL; INTERMEDIATE VALUE
C
C
C     **** PROGRAMMER / DAWN RIGBY ****
C     **** DATE / 22/06/82 ****
C
C
      FUNCTION FACTOR(N)
      IMPLICIT REAL*8(A-H, O-Z)
      FACTOR = 1.
      IF(N-1)40,40,13
   13 IF(N-10)21,21,31
   21 DO 23 I=2,N
      FI = I
   23 FACTOR = FACTOR * FI
      GO TO 40
   31 SUM = 0.
      DO 34 I=11,N
      FI = I
   34 SUM = SUM + DLOG(FI)
      FACTOR = 3628800.*DEXP(SUM)
   40 RETURN
      END
```

```
C
C
C      **** FUNCTION TPROB ****
C
C      ---- THIS FUNCTION FINDS THE VALUE OF 'T' FROM A 'T' ----
C           DISTRIBUTION OF 'NFREE' DEGREES OF FREEDOM, WHICH IS EXCEEDED
C           WITH PROBABILITY ALPHA (2 SIDED TEST).  A TABLE IS USED AS A
C           DATA ARRAY AND INTERPOLATION IS OFTEN NECESSARY TO GET THE
C           CORRECT VALUE OF TPROB.  THE TABULATED DATA WAS COMPUTED BY
C           MAXINE MERRINGTON, FROM "TABLES OF PERCENTAGE POINTS OF THE
C           INCOMPLETE BETA FUNCTION",BIOMETRIKA,VOL.32 (1941),PAGES 168-
C           181; BY CATHERINE M. THOMPSON.
C
C
C      **** USAGE ****
C
C      ---- RESULT = TPROB(FREE,ALPHA) ----
C
C
C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
C
C      ---- NONE ----
C
C
C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
C
C      ---- PARAMETERS PASSED FROM THE MAINLINE ----
C
C           FREE/ REAL; NUMBER OF DEGREES OF FREEDOM
C           ALPHA/ REAL; CONFIDENCE LEVEL OF THE FIDUCIAL LIMITS
C
C      ---- VARIABLES ----
C
C           T/ REAL; ARRAY FOR T DISTRIBUTION TABLE
C           A/ REAL; 1-ALPHA, FOR READING OF THE TABLE AND CALCULATIONS
C           I,J/ INTEGER; LOOP COUNTERS AND ARRAY POINTERS
C           AK,AJK,H,YK,YJK,DY,TI,TIA,FR/ REAL; INTERMEDIATE VALUES
C           FARRAY/ REAL; ARRAY FOR INTERPOLATED FREE VALUES WHEN BOTH
C                   FREE AND A MUST BE INTERPOLATED
C
C
C      **** PROGRAMMER / DAWN RIGBY ****
C      **** DATE / 22/06/82 ****
C      **** Updated / John McFee ****
C      **** DATE / 26/02/86 ****
C
C
       FUNCTION TPROB(FREE,ALPHA)
       IMPLICIT REAL*8(A-H, O-Z)
       DIMENSION T(35,8),FARRAY(7)
       data itabledev/4/
       READ(itabledev,1)((T(J,I),I=1,8),J=1,35)
1      FORMAT(8F10.5)
       A = 1.0D0 - ALPHA
       FR=FREE
C
C      ---- CHECK FOR OUT OF RANGE 'A' OR 'FREE' VALUES ----
```

```
C
      IF(A.LT.0.005)GO TO 3
      IF(A.GT.0.50)GO TO 5
      GO TO 7
 3    write(ioutdev,2)
 2    FORMAT(//3X,'SUBROUTINE TPROB--')
      write(ioutdev,9)
 9    FORMAT(3X,'ALPHA IS GREATER THAN 0.995, THEREFORE, ASSUME THAT ALP
     1HA IS EQUAL TO 0.995')
      A=0.005
      GO TO 7
 5    write(ioutdev,2)
      write(ioutdev,11)
 11   FORMAT('1','ALPHA IS LESS THAN 0.50 -- ERROR ')
      GO TO 34
 7    IF(FR.GT.120.0)GO TO 13
      IF(FR.LT.1.0)GO TO 15
      GO TO 17
 13   write(ioutdev,2)
      write(ioutdev,19)
 19   FORMAT(3X,'THE NUMBER OF DEGREES OF FREEDOM IS GREATER THAN 120.0;
     1'/10X,'THEREFORE ASSUMED TO BE INFINITE')
      FR = 900.
      GO TO 17
 15   write(ioutdev,2)
      write(ioutdev,21)
 21   FORMAT('1','FREE IS LESS THAN 1.0 -- ERROR ')
      GO TO 34
 17   IF(FR.LE.30.0)GO TO 23
      GO TO 25
 23   DO 27 I=2,8
      IF(T(1,I).NE.A)GO TO 27
C
C     ---- FREE AND A ARE BOTH ON TABLE ----
C
      TPROB = T(FR+1,I)
      GO TO 33
 27   CONTINUE
C
C     ---- A IS NOT ON TABLE ----
C
 28   DO 31 I=2,8
      IF(T(1,I).LT.A)GO TO 35
 31   CONTINUE
 35   AK=T(1,I)
      I=I-1
      AJK=T(1,I)
      H=AJK-AK
      YJK=T(FR+1,I)
      YK=T(FR+1,I+1)
      DY=YJK-YK
      TPROB = (DY * (A-AK)/H) +YK
      GO TO 33
C
C     ---- FREE IS GREATER THAN 30.0 ----
C
 25   DO 37 J=31,35
```

```
              IF(T(J,1).NE.FR)GO TO 37
              DO 75 I=2,8
              TI=T(1,I)
              TIA = TI - A
              IF(TIA.LT.1.0D-13) GO TO 76
       75     CONTINUE
              GO TO 28
      C
      C       ---- FREE > 30.0; FREE AND A BOTH ON TABLE ----
      C
       76     TPROB = T(J,I)
              GO TO 33
       37     CONTINUE
       39     DO 41 I=2,8
              IF(T(1,I).NE.A)GO TO 41
      C
      C       ---- FREE IS NOT ON TABLE ----
      C
              DO 42 J=31,35
              IF(T(J,1).GT.FR)GO TO 45
       42     CONTINUE
       41     CONTINUE
              GO TO 43
       45     AK=T(J,1)
              J=J-1
              AJK=T(J,1)
              H=AJK-AK
              YJK=T(J,I)
              YK=T(J+1,I)
              DY=YJK-YK
              TPROB = (DY * (FR-AK)/H) +YK
              GO TO 33
      C
      C       ---- NEITHER FREE NOR A ARE ON TABLE ----
      C
       43     DO 47 J=31,35
              IF(T(J,1).GT.FR)GO TO 49
       47     CONTINUE
       49     AK=T(J,1)
              J=J-1
              AJK=T(J,1)
              H=AJK-AK
              DO 51 I=2,8
              YJK=T(J,I)
              YK=T(J+1,I)
              DY=YJK-YK
              TPROB = (DY * (FR-AK)/H) + YK
              FARRAY(I-1)=TPROB
       51     CONTINUE
              DO 53 I=2,8
              IF(T(1,I).LT.A)GO TO 55
       53     CONTINUE
       55     AK=T(1,I)
              I=I-1
              AJK=T(1,I)
              H=AJK-AK
              YK = FARRAY(I-1)
```

```
      YJK = FARRAY(I-2)
      DY=YJK-YK
      TPROB = (DY * (A-AK)/H) + YK
      GO TO 33
34    STOP
33    RETURN
```

APPENDIX 6

OPERATIONAL DESCRIPTION OF RELATIVE POTENCY PROGRAM RPOTC

RELATIVE POTENCY PROGRAM (RPOTC)

--- Revised Edition -- Account BI000200,STATS,DRES ---

Dawn Rigby -- June, 1983

INPUT:

The RPOTC program has now been transferred to the Honeywell CP-6 computer system, and some changes in input are therefore required. The data is typed interactively (excluding the chisq and t table) and read directly by the command file. Each value is asked for separately, so that carriage returns separate the data. The values are as follows.

ISLCT - select value. If ISLCT=1, 6 sets of numbers must follow (limit, lowest datum, and highest datum for each set). This indicates that limits other than 95% (ISLCT=0) are to be used. If a -1 is typed, execution terminates.

LIMIT - percentage limits to be used (integer)

INUM - number of comparisons to be made in the set

I - lowest datum

J - highest datum

ICODE - identification code

CHISQ,SNW,XBAR,SXX,SXY,DFREE,YBAR,SYY - results of the PROBIT analysis

EXECUTION

At this time, the mainline RPOTC program is in the file KEEP_RPOTC, and the command file to run this is called RPOTC. These files MUST NOT be deleted under any circumstances. The compilation and linkage files are called RPOTC_OU and RPOTC_RU. These should also be left alone, but can be replaced by typing the following:

FORTRAN KEEP_RPOTC OVER RPOTC_OU

LINK RPOTC_OU OVER RPOTC_RU

To execute this program, type:

XEQ RPOTC

The program and additional files are all in the acount 3I000200,STATS,DRES.

OUTPUT

The output for this program has not been changed, and is sent to both the terminal and the line printer immediately after execution.

TABLE 1

Initial Data for Program PROBIT

ID - array for the identification label (to begin each page)
format: alphabetic; maximum of 50 characters

NT - number of trials, maximum of 100 (n)
MAXCNT - maximum loop count for iterative regression (default = 50)
format: integer; NT, MAXCNT are entered on the same line.

IYNSW - switch for output of intermediate results
YES - IY, output requested
NO - IN; no output requested
format: alphanumeric; maximum of 50 characters

TN - number of animals in the trial (n_i)
XIN - dose given in the trial (x_i')
R - number of responses in the trial, maximum of 100 (r_i)
format: real; TN, XIN, R are entered on the same line, 1 trial/line

ALPHA - confidence level of fiducial limits (default = 0.95), ($\alpha/100$)
format: real

C - fraction of natural mortality (default = 0.0) (P_0)
DELTA - convergence criterion (default = 0.001) (δ)
format: real; both C and DELTA typed on the same line

TABLE 2

Quantities Output by Program PROBIT

I	- integer; trial number (i)
J	- integer; loop number (k)
X	- real; dose metameters (x_i)
RP	- real; empirical percentage responses (P_i*100)
RS	- real; mean of estimated number responding ($\hat{R}_i$)
YK	- Real; maximum likelihood expected NEDS ($y(x_i)$)
YR	- real; probits (NEDS + 5)
SIGY	- real; standard error
W	- real; weighting coefficient ($w_i^{(k)}$)
B	- real; current regression slope ($a_1^{(k)}$)
SIGMAB	- real; error in regression slope ($S_{a1}^{(k)}$)
FLY	- real; lower fiducial limits of estimated number responding
FUL	- real; upper fiducial limits of estimated number responding
CHISQ	- real; value of chi square ($\chi^2_\alpha(\nu)$)
NFREE	- integer; number of degrees of freedom (ν)
H	- real; heterogeneity factor (h)
	H = 1.0 --- homogeneous
	H $\neq$ 1.0 --- deterogeneous
T	- real; value of T distribution (t_α)
G	- real; G factor (g)
PLB	- real; given ED levels (dose level * 100) (P_λ)
EDLMB	- real; tolerance level in dose units (ED_λ)
XLMBDA	- real; tolerance level in dosage units (x_λ)
FUED	- real; upper fiducial limit for EDLMB ($f'_{u\lambda}$)
FLED	- real; lower fiducial limit for EDLMB ($f'_{l\lambda}$)
FUX	- real; upper fiducial limits for XLMBDA ($f_{u\lambda}$)
FLX	- real; lower fiducial limits for XLMBDA ($f_{l\lambda}$)
APA	- real; percent confidence level (α)

TABLE 3

Data for Comparison Tests of Programs PROBIT and PROBT

Dose (Relative Units)	Organisms	Responses
Series 1		
400.	10	7
320.	10	1
256.	10	0
204.	10	1
163.	10	0
Series 2		
400.	10	8
320.	10	4
256.	10	1
204.	10	1
163.	10	0
Series 3		
400.	10	9
320.	10	5
256.	10	1
204.	10	1
163.	10	0
Series 4		
140.	20	17
130.	20	6
120.	20	7
110.	10	5
100.	20	1
Series 5		
180.	10	10
170.	10	7
160.	20	11
150.	15	7
140.	10	3
130.	5	0
120.	10	1

Dose (Relative Units)	Organisms	Responses
Series 6		
150.	20	19
140.	30	26
130.	40	29
120.	50	27
110.	40	14
100.	30	6
80.	20	0
Series 7		
499.	10	4
474.	10	5
450.	20	6
427.	10	1
406.	10	0
405.	10	1
364.	10	1
327.	10	0
Series 8		
499.	10	6
474.	10	6
450.	20	6
427.	10	1
406.	10	0
405.	10	2
364.	10	1
327.	10	0
Series 9		
499.	10	6
474.	10	6
450.	20	7
427.	10	1
406.	10	0
405.	10	2
364.	10	1
327.	10	0

UNCLASSIFIED

TABLE 4

Results of Comparison Tests of Programs PROBIT and PROBT

Series	Program	ν	Reduced Chi-square	Data Heter- ogenous	a_1	S_{a_1}	g	ED_{50}	$f'_{l_{50}}$	$f'_{u_{50}}$	ED_{95}	$f'_{l_{95}}$	$f'_{u_{95}}$	Con- vergence	Iter- ations
1.	PROBIT	3	7.66	No	3.36	1.14	0.445	385.	333.	594.	629.	471.	2453.	Yes	5
	PROBT	2	3.82	Yes	3.35	2.23	0.444	385.	∞	∞	-	-	-	Yes	5
2.	PROBIT	3	1.61	No	3.58	0.98	0.287	332.	292.	406.	526.	423.	1019.	Yes	3
	PROBT	2	0.80	No	3.58	0.98	-	332.	292.	406.	-	-	-	Yes	3
3.	PROBIT	3	2.09	No	4.20	1.07	0.248	313.	278.	362.	463.	390.	732.	Yes	3
	PROBT	2	1.04	No	4.20	1.06	-	313.	278.	362.	-	-	-	Yes	4
4.	PROBIT	3	12.56	Yes	5.52	2.69	2.41	127.	-	-	172.	-	-	Yes	3
	PROBT	3	4.18	Yes	5.51	2.68	-	127.	29.3	1150	-	-	-	Yes	12
5.	PROBIT	5	3.71	No	6.99	1.57	0.193	153.	145.	161.	194.	179.	234.	Yes	5
	PROBT	5	0.75	No	6.98	1.56	-	153.	145.	160.	-	-	-	Yes	9
6.	PROBIT	5	0.626	No	6.11	0.80	0.066	117.	113.	121.	153.	145.	168.	Yes	3
	PROBT	5	0.126	No	6.11	0.80	-	117.	113.	120.	-	-	-	Yes	7
7.	PROBIT	6	4.389	No	5.74	1.84	0.394	503.	470.	633.	670.	568.	1351.	Yes	4
	PROBT	5	0.876	No	5.74	1.83	-	502.	470.	633.	-	-	-	No	41
8.	PROBIT	6	5.329	No	6.77	1.88	0.294	481.	458.	541.	613.	544.	905.	Yes	4
	PROBT	5	1.064	No	6.77	1.87	-	480.	457.	540.	-	-	-	Yes	17
9.	PROBIT	5	5.021	No	6.86	1.86	0.282	477.	455.	531.	607.	541.	871.	Yes	4
	PROBT	5	1.00	No	6.85	1.85	-	477.	455.	530.	-	-	-	Yes	19

TABLE 5

Data for Comparison Tests of Programs PROBIT, S103 and SAS

Dose (Relative Units)	Organisms	Responses
Series 1		
6374.	10	10
5951.	10	8
5371.	10	1
4975.	10	2
4522.	10	2
4048.	10	0
3674.	10	1
3312.	10	0
Series 2		
5951.	10	10
4975.	10	7
4522.	10	7
4048.	10	0
Series 3		
6374.	10	4
5951.	10	1
5371.	10	1
4975.	10	1
4522.	10	0
4048.	10	0
3674.	10	0
3312.	10	0
Series 4		
6374.	10	10
5951.	10	10
5371.	10	3
4975.	10	6
4522.	10	2
4048.	10	0
3674.	10	1
3312.	10	0

Dose (Relative Units)	Organisms	Responses
Series 5		
6374.	10	10
5971.	10	10
5371.	10	2
4975.	10	3
4522.	10	2
4048.	10	0
3674.	10	1
3312.	10	0
Series 6		
50.	10	9
40.	10	8
32.	10	9
25.	10	0
Series 7		
650.	10	10
585.	10	10
526.5	10	6
473.9	10	2
426.5	10	3
Series 8		
222.	10	10
200.	10	3
180.	10	2
162.	10	0
146.	10	0
131.	10	0
118.	10	0
106.	10	0
Series 9		
585.	10	10
526.5	10	6
473.9	10	2
426.5	10	3

TABLE 6

Results of Comparison Tests of Programs PROBIT, S103 and SAS

Series	Program	ν	Reduced Chi-square	Data Heter-ogenous	a_1	S_{a_1}	g	ED_{50}	$f'_{l_{50}}$	$f'_{u_{50}}$	ED_{95}	$f'_{l_{95}}$	$f'_{u_{95}}$	Con-vergence	Iter-ations
1.	PROBIT	6	17.25	Yes	5.89	2.12	0.779	5447.	4533.	8483.	7204.	6028.	80395.	Yes	5
	S103	6	17.24	Yes	5.88	2.12	0.780	5447.	4533.	8487.	7204.	6028.	80610	-	20
	SAS	6	17.25	Yes	5.88	2.05	-	5447.	4630.	8401.	7203.	6005.	51108.	Yes	6
2.	PROBIT	2	4.56	No	11.04	3.26	0.335	4571.	4319.	4845.	5306.	4961.	6605.	Yes	7
	S103	2	4.56	No	11.04	3.26	0.355	4571.	4319.	4845.	5305.	4960.	6604.	-	20
	SAS	2	4.56	No	11.04	3.36	-	4571.	4299.	4831.	5306.	4968.	6640.	Yes	7
3.	PROBIT	6	1.91	No	5.08	2.06	0.633	6953.	6209.	15328.	9613.	7558.	73752.	Yes	5
	S103	6	1.91	No	5.08	2.06	0.633	6952.	6209.	15290.	9612.	7557.	73350	-	20
	SAS	6	1.91	No	5.08	2.07	-	6953.	6207.	15709.	9613.	7549.	78263.	Yes	6
4.	PROBIT	6	14.14	Yes	6.77	1.98	0.512	5043.	4349.	5877.	6430.	5632.	12292.	Yes	5
	S103	6	14.14	Yes	6.77	1.98	0.512	5043.	4349.	5877.	6429.	5631.	12290	-	20
	SAS	6	14.15	Yes	6.77	1.98	-	5043.	4387.	5936.	6429.	5616.	12464.	Yes	6
5.	PROBIT	6	18.86	Yes	6.70	2.36	0.745	5222.	4220.	6903.	6675.	5732.	34786.	Yes	6
	S103	6	18.84	Yes	6.70	2.36	0.744	5221.	4222.	6897.	6675.	5731.	34500	-	20
	SAS	6	18.86	Yes	6.70	2.31	-	5222.	4368.	7077.	6675.	5706.	29259.	Yes	6
6.	PROBIT	2	9.15	Yes	3.90	2.35	6.68	31.11	-	-	47.41	-	-	Yes	7
	S103	2	9.16	Yes	3.90	2.35	6.68	31.11	-	-	47.40	-	-	-	20
	SAS	2	9.15	Yes	3.90	2.31	-	31.10	-	-	47.41	-	-	No	6
7.	PROBIT	3	5.31	No	7.65	1.87	0.231	490.0	455.4	520.1	607.6	561.6	737.8	Yes	6
	S103	3	5.31	No	7.65	1.87	0.231	490.0	455.4	520.2	607.7	561.6	737.9	-	20
	SAS	3	5.31	No	7.65	1.88	-	490.0	457.1	521.1	607.6	560.1	745.6	Yes	6
8.	PROBIT	6	4.03	No	12.65	3.36	0.271	199.2	189.8	209.8	226.9	214.0	265.8	Yes	8
	S103	6	4.03	No	12.65	3.36	0.271	199.2	189.8	209.8	226.9	214.0	265.8	-	20
	SAS	6	4.04	No	12.66	3.43	-	199.2	190.2	210.6	226.8	213.5	269.6	Yes	8
9.	PROBIT	2	4.78	No	7.15	2.09	0.328	491.3	453.6	527.4	618.4	562.5	843.7	Yes	5
	S103	2	4.78	No	7.15	2.09	0.328	491.3	453.6	527.4	618.4	562.5	843.7	-	20
	SAS	2	4.78	No	7.15	2.10	-	491.3	455.6	529.4	618.4	560.9	855.7	Yes	5

ADA171509

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1 ORIGINATING ACTIVITY DEFENCE RESEARCH ESTABLISHMENT SUFFIELD RALSTON, ALBERTA	2a. DOCUMENT SECURITY CLASSIFICATION unclassified 2b. GROUP

3 DOCUMENT TITLE

"PROBIT": A PROBIT ANALYSIS PROGRAM FOR THE DRES COMPUTER FACILITY (U)

4 DESCRIPTIVE NOTES (Type of report and inclusive dates)
SUFFIELD REPORT 403

5. AUTHOR(S) (Last name, first name, middle initial)

J. McFee, C.E. Mendoza, J. Smith and D. Rigby

6 DOCUMENT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
July 1986	77	8

8a. PROJECT OR GRANT NO. 051SB	9a. ORIGINATOR'S DOCUMENT NUMBER(S) SUFFIELD REPORT 403
8b CONTRACT NO.	9b. OTHER DOCUMENT NO.(S) (Any other numbers that may be assigned this document)

10. DISTRIBUTION STATEMENT

UNLIMITED

11 SUPPLEMENTARY NOTES	12. SPONSORING ACTIVITY

13. ABSTRACT

This report describes an interactive computer program PROBIT, which performs automated probit analysis. The code is written in the FORTRAN IV language using a modified iterative maximum likelihood algorithm and runs on the Honeywell DPS-8/70 and VAX 11/780 computers.

A series of tests were performed to compare PROBIT with other probit analysis programs. These include the old DRES PROBT (modified IBM PROBT) and programs contained in the commerical statistical packages S103 and SAS. PROBIT clearly outperformed DRES PROBT and performed as well as S103 and as well or slightly better than SAS.

The input methods and output format of PROBIT can be modified whereas those of most commerical statistical packages cannot. Finally, PROBIT cost substantially less to develop than the purchase price of typical commerical statistical packages containing a good probit analysis program.

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